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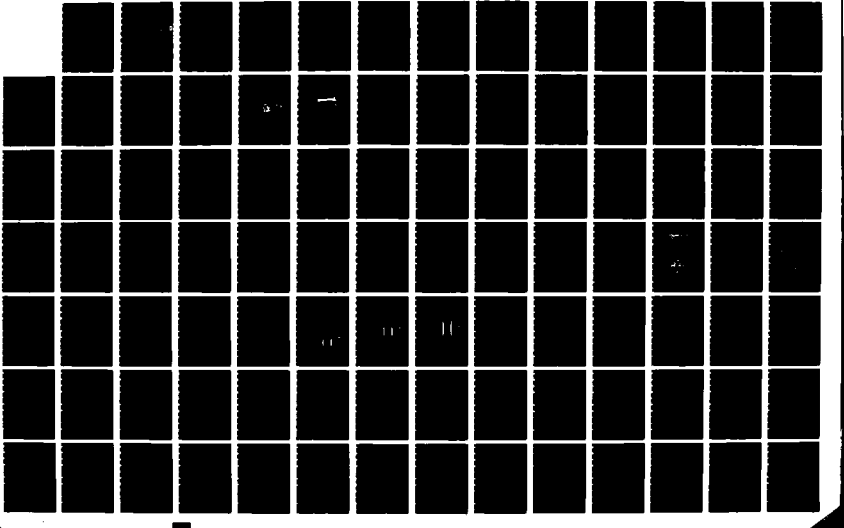

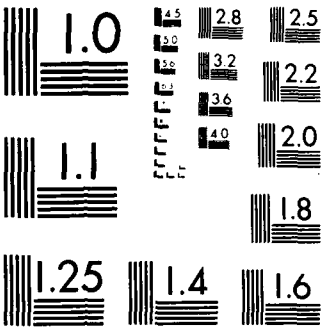

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The Effect of an Experimental Missile Wound to the Brain on Brain Electrolytes, Regional Cerebral Blood Flow and Blood Brain Barrier Permeability

Annual Final Report

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10 February 1987

(From 1 July 1983 Through 31 December, 1985)

U.S. Army Medical Research and Development Command

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19 ABSTRACT (Continue on reverse if necessary and identify by block number)

Brain wounds account for most deaths on the battlefield yet scarcely any research has been done on brain wounds caused by missiles. We have developed a laboratory model for painlessly creating a uniform brain wound in anesthetized cats and have studied several physiologic variables altered by brain wounding. Brain wounds of higher energies often cause apnea which may be fatal without respiratory support but which may be temporary and reversible provided respiratory support is given. Brain wounding is associated with a moderate degree of vasogenic brain edema, maximal 24-48 hours after wounding. Following this it begins to recede. Brain wounding is associated with immediate and large rises of prostaglandins in the cerebrospinal fluid. Prostaglandins may add to brain damage directly by affecting neurons themselves or indirectly by producing ischemi. Neurologic deficits from brain wounding were maximal within the first two days and tended to improve thereafter.

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SUMMARY:

Brain wounds account for most deaths on the battlefield yet scarcely any research has been done on brain wounds caused by missiles. The purpose of this research was to develop a valid laboratory model of a brain wound and to study several clinically important physiologic variables altered by wounding. Better adjunctive medical treatments for brain wounds will be developed once the pathophysiology of brain wounding is understood.

We have developed a laboratory model for painlessly creating a uniform brain wound in anesthetized cats and have studied several physiologic variables altered by brain wounding. We make the brain wound by a helium powered gun which fires a 2mm diameter, 31mg, steel sphere across a velocity gate and through a cat's intact skull. Prior to wounding, the cat is precisely positioned in front of the gun in a stereotaxic frame. Missile energy is calculated from measured velocity.

Our main results are as follows:

1) Brain wounds of higher energies often cause apnea which may be fatal without respiratory support but which may be temporary and reversible provided respiratory support is given. THESE FINDINGS MAY HAVE THE UTMOST CLINICAL IMPORTANCE: POSSIBLY, MANY SOLDIERS WHO RECEIVE "FATAL" BRAIN WOUNDS DIE BECAUSE OF RESPIRATORY ARREST RATHER THAN FROM INTRINSICALLY FATAL BRAIN DAMAGE PER SE. POSSIBLY THE LIVES OF MANY SOLDIERS WITH BRAIN WOUNDS MIGHT BE SAVED WITH A BRIEF PERIOD OF RESPIRATORY SUPPORT.

2) Brain wounding is associated with a moderate degree of vasogenic brain edema, maximal 24-48 hours after wounding. Following this it begins to recede. In uncomplicated cases the associated brain edema may need no treatment.

3) Brain wounding is associated with immediate and large rises of prostaglandins in the cerebrospinal fluid. Prostaglandins may add to brain damage directly by affecting neurons themselves or indirectly by producing ischemia.

4) Neurologic deficits from brain wounding were maximal within the first two days and tended to improve thereafter. Seven to 14 days later brain-wounded cats appeared quite normal.

5) We have developed a model of brain wounding whereby the pathophysiology and associated perterbations of animal behavior consequent to wounding can be studied acutely and chronically. By means of this system we may test drugs to see whether they improve brain function and animal behavior after a brain wound.

FOREWORD:

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

The experiments presented in this report were performed by Gurcharan S. Sarna, PhD. and J. Bryan Farrell, BS.

The triggering and timing circuits were modified by Leo T. Happel, Jr., PhD.

This manuscript was typed by Mrs. Elizabeth P. Hulbert

Note that cerebral blood flow studies were not actually performed in this contract period owing to laboratory start up time and DOD-ordered suspension of research for 5 months of this contract period.

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page no.

This report documents the work done on U.S. Army contract DAMD-83-C-3145 entitled The Effects of an Experimental Missile Wound to the Brain on Brain Electrolytes, Regional Cerebral Blood Flow and Blood Brain Barrier Permeability which ran from 1 July 1983 through 31 December 1985.

1. BACKGROUND

Review of combat medical statistics reveals no significant reduction in neurosurgical mortality of brain wounds from WWII through the Vietnam experience(1), figure 1.

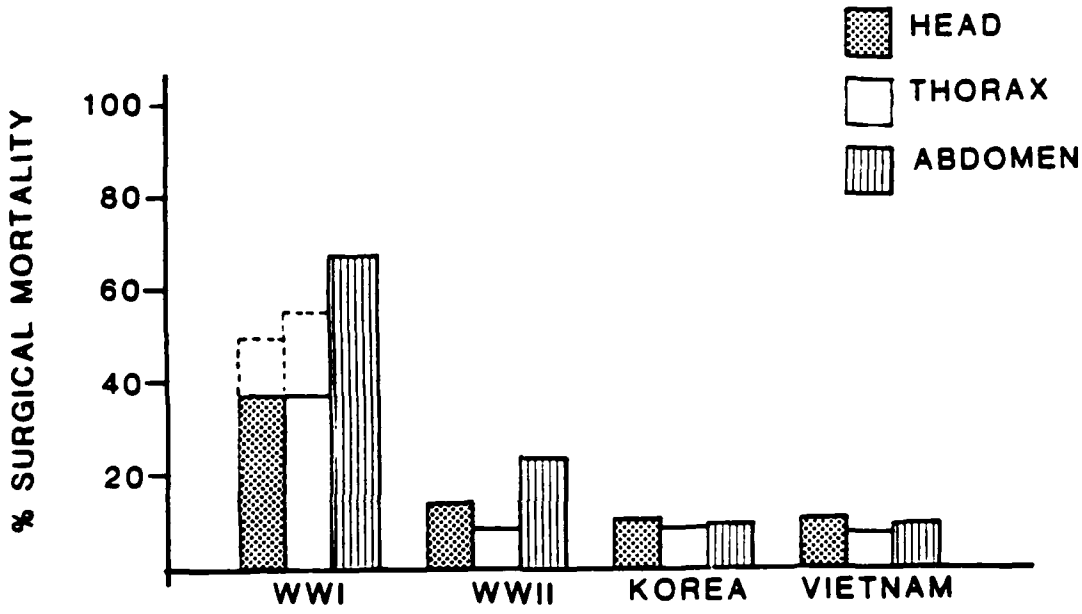


Figure 1: The postoperative mortality of head wounds has remained relatively unchanged since World War II. The best postoperative mortality for head wounds reported during World War II was 11%, essentially the same reported from Vietnam.(1,2,3)

In order to learn how to treat brain wounds better on the battlefield we have developed an experimental model of a brain wound in the cat so we can study physiological dysfunction associated with brain wounding. We will then be able to learn how to use medications or technology to correct these physiological dysfunctions. This knowledge should lead to: 1) better treatment of brain wounds sustained in combat; 2) lessened mortality and morbidity and 3) a greater rate of return of brain-wounded soldiers to some form of Army duty, thus conserving the fighting strength.

2. LABORATORY GUN

In sustained combat, shell or other fragments cause about three quarters of all wounds.(4) Approximately 90 percent of all survivable brain wounds (neurosurgical wounds) seen in combat are caused by fragments.(2,3) In order to create an experimental brain wound we have developed a helium-powered laboratory gun capable of firing a small, 31mg steel sphere at different velocities and wounding energies: ($E=1/2\ mv^2$; m=missile mass, v= missile velocity). The missile fired simulates a fragment. In our laboratory gun a helium gas charge, contained at a specified pressure within a storage tank, is released by a solenoid valve to propel the experimental missile through the gun barrel. Missile speed is measured by passage through electronic screens. The wounding energy of the missile is expressed in Joules (J). Figure 2 is a diagram of the experimental gun and animal set-up. Perusal of figure 3 indicates that with this experimental laboratory gun missile velocities are very reproducible for any given helium pressure charge.

Schematic Illustration of Experimental Layout

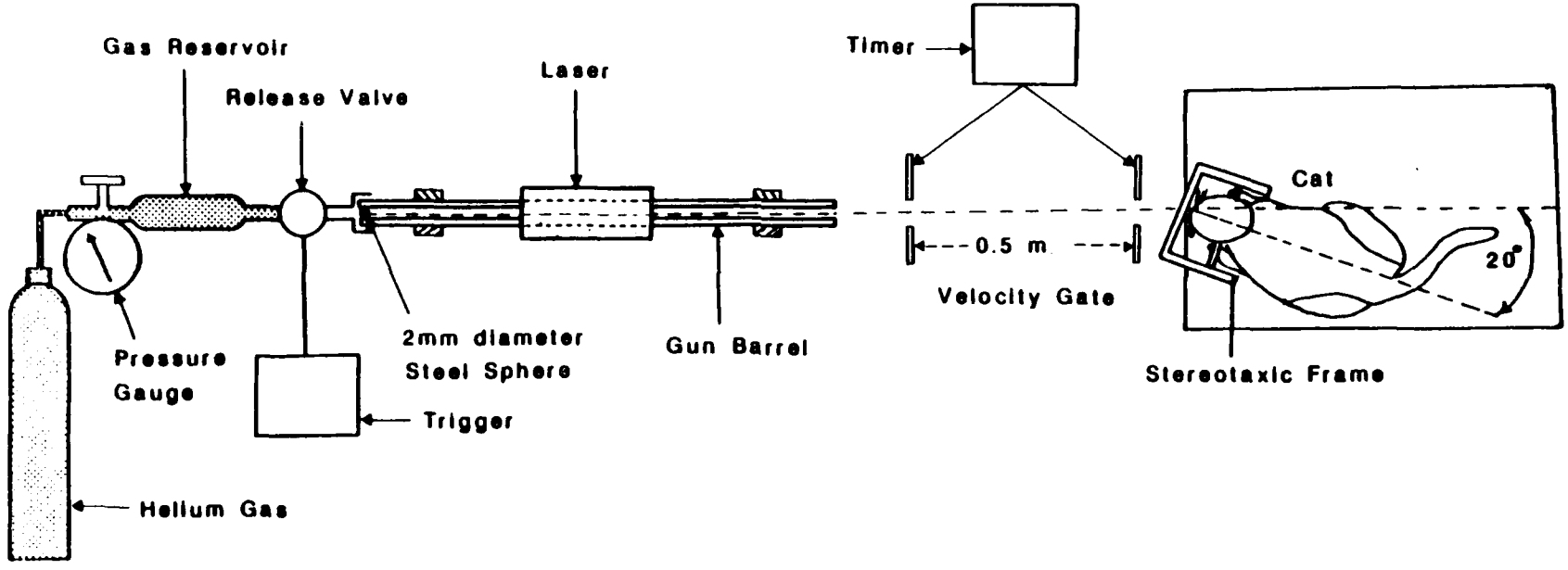


Figure 2: Schematic of experimental set-up. A helium charge propels the 2mm steel sphere through the gun barrel. The missile passes through the timing gates and into the cat's right cerebral hemisphere.

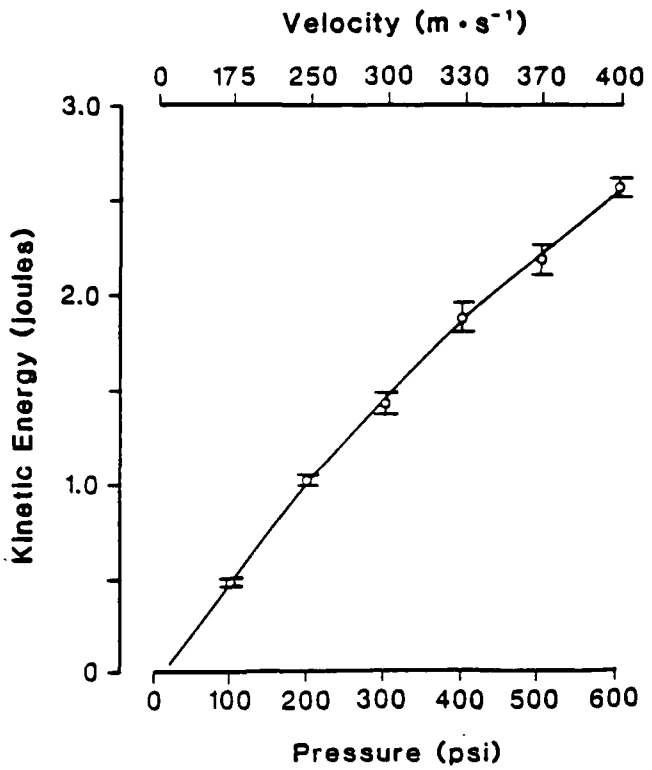


Figure 3: Shooting pressure is plotted against missile velocity and energy. Each point represents the mean velocity of 5 shots ± the S.D. Note that 0.5 to 0.7 Joules of energy are required to achieve frontal bone penetration while 2.4 Joules is uniformly fatal owing to respiratory arrest. Thus, the ballistics limits for creation of a non-fatal brain wound in this model are fairly narrow: from about 0.9 to 2.0 Joules.

The gun initially supplied to us by its manufacturer (Mr. Robert Carpenter, formerly of the Edgewood Arsenal, Edgewood, Md 21010) fired erratically. Missile trajectory was greatly improved with new, specially made, precision-milled barrel liners and a new outer barrel design which allowed the barrel liners to be seated in the barrel without any induced liner bending. This non-rifled gun is sufficiently accurate at the 80cm target distance to enable projectiles to strike a specific tissue target within a few millimeters of the aiming point.

The commercial timer originally supplied to us was unable to time the pellet fired through the timing screens because these screens are only 0.5m apart. Since substituting a precision time base we have been able to time missile passage between timing screens very accurately. Circuitry for the time base is given in figure 4.

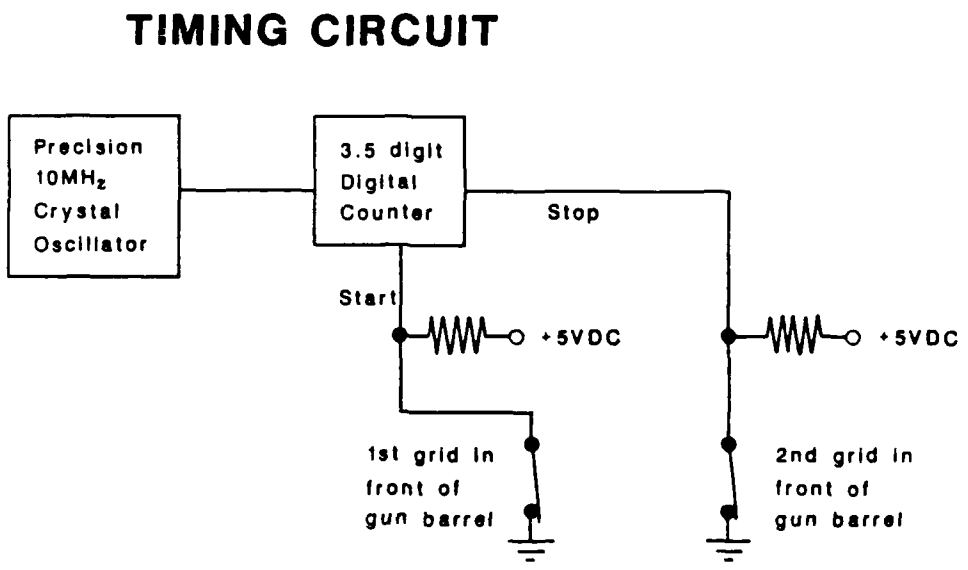


Figure 4: The timing circuit to measure missile velocity consists of a time base and a precision 10mHz crystal oscillator driving a 3.5 digit counter. The small silver break screen grids through which the missile passes serve as a switch to start and stop the counter. The grids are exactly 0.5m apart. When the missile breaks the first screen the counter begins counting 10mHz pulses because the start line is biased through a resistor. When the projectile breaks the second grid this opens the switch which biases the stop line. The time interval between screen breaks is measured by the number of pulses from the oscillator counted by the digital counter. When both start and stop lines are grounded counting is disabled and the counter can be reset to zero.

The triggering mechanism supplied by the manufacturer used alternating current (AC) from an ordinary 110V electric outlet. With this triggering mechanism we often obtained the same missile velocity whether we fired at 300 or 600 pounds per square inch (psi) shooting pressure. Because of AC current, our system often required several milliseconds for the charge to build up enough to effect solenoid valve* release, depending upon at what point in the AC cycle the trigger was pressed. This gradual charge build up sometimes caused the solenoid valve to be released slowly, often sending a helium pulse of varying intensity to the pellet in the gun thus giving erratic pellet speeds. Deducing this difficulty, we substituted a triggering mechanism that used a direct current (DC) power source which applied 600 volts to the solenoid valve situated between the helium chamber and the gun barrel, figure 5.

TRIGGER CIRCUIT

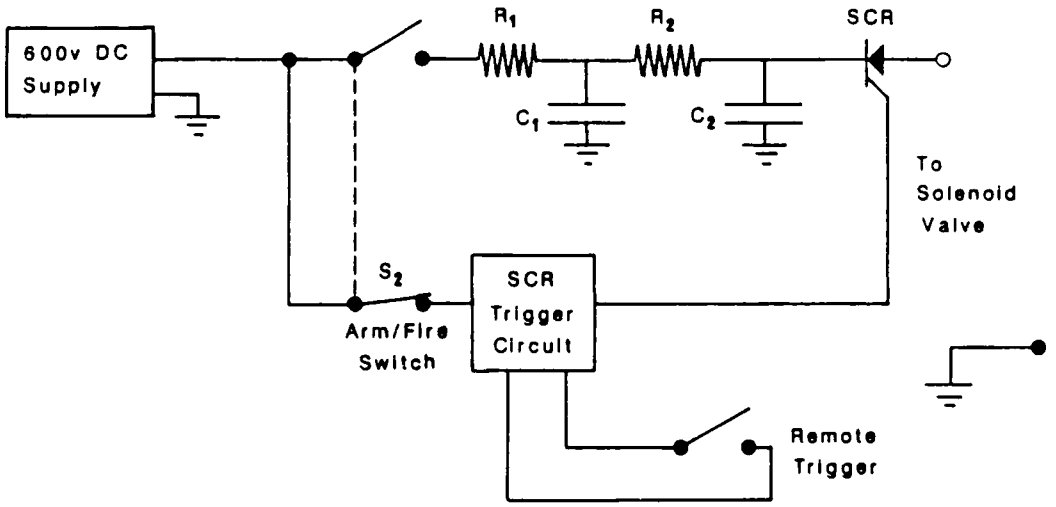


Figure 5: The triggering circuit is powered by a 600 volt DC power source which charges capacitors C1 and C2 when the arm/fire switch is in the "arm" position. After the capacitors are charged the arm/fire switch is thrown to the "fire" position which allows the trigger circuit to fire the silicon controlled rectifier (SCR). The remote trigger activates the SCR and discharges capacitor C1 and C2 into the winding of the solenoid valve lifting the gate mechanism. Capacitor C2 supplies most of the initial current surge needed to open the valve. Capacitor C1 discharges more slowly because of resistor R2 and this extends the times that the valve remains open ensuring adequate helium discharge.

This arrangement has allowed great reproducibility of missile velocity with each shooting pressure. With the DC triggering mechanism and the 600 volt valve opening impetus, a uniform initial helium charge is instantaneously applied to the pellet at each shooting pressure. This has resulted in very small standard deviations in missile velocity at each shooting pressure, figure 3.

* Model 16200S0R Atkomatic Valve Co., Inc., Indianapolis, Indiana

Our realizing the need for these modifications to make the gun accurate with a precise timing device and the time needed for fabrication of the new barrel liners by the factory consumed most of the first 6 months of our initial contract period. Our laboratory gun is now highly perfected and we have used it successfully in more than 250 experiments in the past 21 months.

3. ANIMAL PREPARATION, WOUNDING AND SACRIFICE

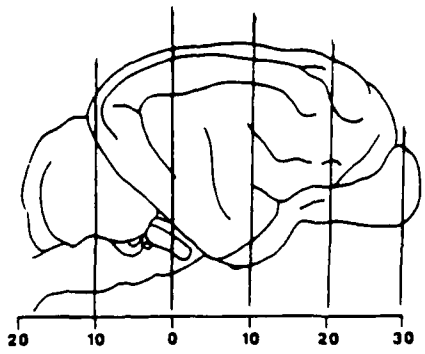
We have used unselected mongrel cats of 3-5kg for our experiments. Operative procedures on the animals were simple, short and uncomplicated. After anesthetic induction with intravenous or intraperitoneal pentabarbital, we made unilateral or bilateral groin incisions 3 to 4cm in length for femoral artery or vein cannulations. In some animals one femoral arterial line was connected to a transducer*-physiograph** for blood pressure recording while the other femoral artery catheter was used for sampling of blood gases, blood electrolytes, or blood glucose. A femoral vein cannula was used for anesthetic administration as needed. After vessel cannulation we closed the groin incisions with skin clips or sutures. Next we applied local anesthetic to the trachea and inserted an endotracheal tube. Tracheal end-expiratory CO_2 was measured by an end-tidal CO_2 monitor*** and recorded on the physiograph. We then placed the cats prone in a stereotaxic frame**** situated 80cm from the muzzle of our helium gun. All cats had a 4 to 5 cm midline frontal skin incision and subsequent removal of the anterior wall of the right frontal sinus. In animals that we planned to measure intracranial pressure, we extended the scalp incision posteriorly and made a 5mm left occipital trephine to insert an epidural pressure transducer***** connected to the physiograph. We sealed the transducer in the skull opening with dental acrylic. At the start of each experiment we made baseline recordings of monitored physiologic variables. After again checking that a satisfactory level of anesthesia was present so the cats would feel no pain, we wounded the cats in the right cerebral hemisphere with the 31mg steel sphere fired from our laboratory gun.

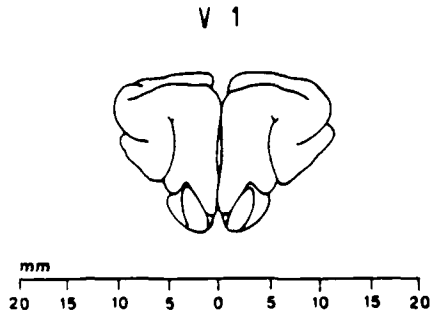
We have maintained cats from 10 minutes to 21 months after wounding depending upon which physiologic or behavioral variable we wished to study. Cats allowed to recover from wounding and anesthesia for behavioral testing were treated with local antibiotic ointment and topical anesthetic to all wounds. We also gave them systemic antibiotics and carefully nursed and observed the animals directly in the laboratory until they had fully recovered. None appeared in any pain. At the appropriate times animals were painlessly euthanized with intravenous pentabarbital and exsanguination. Brains were removed for our various studies.

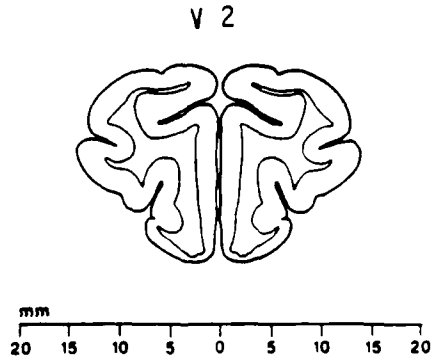
4. STANDARD BRAIN SECTIONS

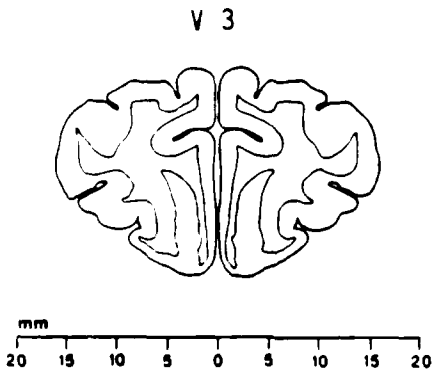
One of our first tasks was to devise a way of sectioning the brains of our experimental animals in a uniform fashion so that the same brain areas could be repetitively sampled in all experiments. We have devised a brain mold to hold cat brains and a multibladed cutting apparatus which allows uniform sectioning of all brains. The mold and cutting blades have been so devised that the cut sections correspond to cat brain sections depicted in the cat brain atlas of Reinoso-Suarez(5). Our "standard brain sections" are shown in figure 6.

* P1000B, Narco Bio-systems, Houston, Tx, 77061
** DMP4A, Narco Bio-systems, Houston, Tx, 77061
*** IL-200, Instrumentation Laboratory, Lexington, Mass, 02173
**** David Kopf Instruments, Tujunga, CA, 91042
***** Gaeltec Ltd, Medical Measurements Inc, Hackensack, NJ, 07601









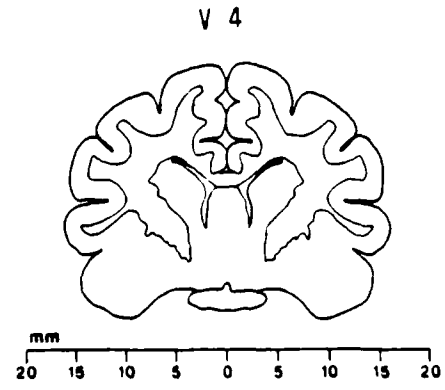
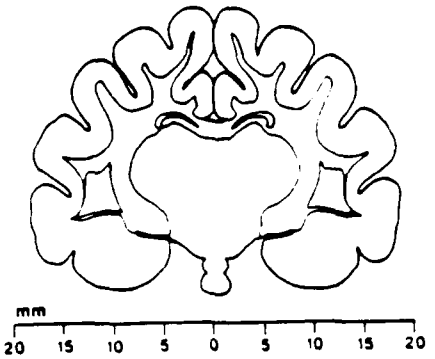
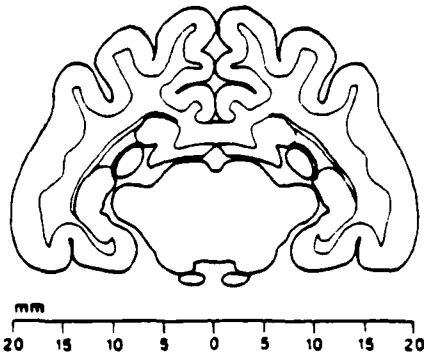


Figure 6: Top picture shows lateral view of cat's brain and plane of coronal sections. Our "standard brain sections" in the coronal plane correspond to various sections depicted in the cat brain atlas of Reinoso-Suarez(5). Our numbers V1 to V10 are arbitrary. Section V-4 is conveniently used to compare missile damage among cats.

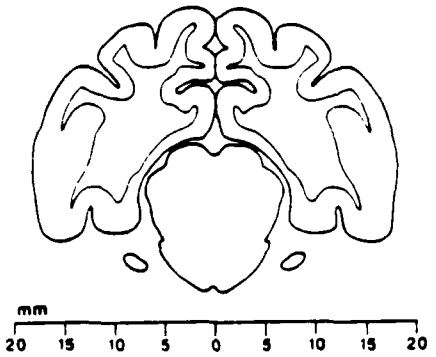
V 5



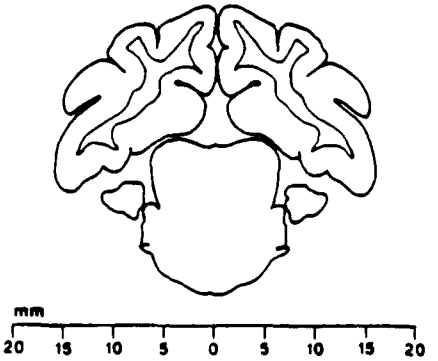
V 6



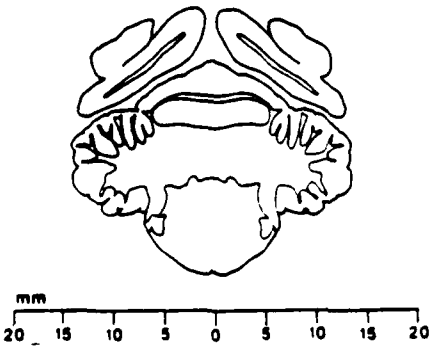
V 7



V 8



V 9



V 10

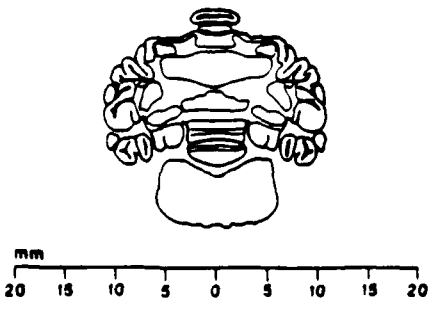


Figure 6 cont'd: Standard brain sections V5 to V10.

5. MISSILE TRAJECTORY

Since the majority of brain wounds in combat enter the anterior part of the skull, we felt it more realistic for our laboratory model to have a frontal entry site for the missile. We selected a right frontal entry site and an anterior-posterior trajectory which confines the experimental missile damage to one hemisphere. The left, contralateral cerebral hemisphere remains undamaged by direct missile injury. The non-wounded hemisphere is, however, subject to overpressures caused by missile passage so the non-damaged hemisphere is not really a true "control" cerebral hemisphere. We, thus, have performed requisite control experiments on operated but unwounded cats to obtain true control brain data.

Initial experiments revealed that the steel sphere glanced off the sloping frontal bone of the cat's skull owing to the bone's inclination and the sphere's light mass. We, therefore, decided to remove the outer wall of the right frontal sinus leaving the posterior sinus wall adjacent to the frontal lobe intact. As the posterior wall of the frontal sinus is not sloped and is at right angles to missile trajectory, the steel sphere readily penetrates the skull and enters the brain. Note that with removal of the outer sinus wall the the inner sinus wall is not disturbed thus the brain remains totally enclosed within an intact skull prior to wounding.

Our initial trajectory was in a straight anterior-posterior direction just to the right of the midline. With this trajectory only a small target area existed above the lateral ventricle and the superior surface of the brain. Intracerebral bleeding tended to dissect down into the ventricle and block cerebrospinal fluid pathways. This often lead to death from acutely increased intracranial pressure. The anterior-posterior trajectory also caused the missile to impact on the bony tentorium directly above the brainstem. While these impacts caused spectacular brainstem effects we considered this feature undesirable because it did not represent the human situation relative to brain wounds. We, therefore, decided to turn the animals' occiputs 20° to the left. Turning of the occiput did not alter the frontal missile entry side appreciably but it effectively put the posterior portion of the missile trajectory into the lateral parietal-occipital lobe of the right cerebral hemisphere, away from the lateral ventricle and brainstem, figures 7 and 8.

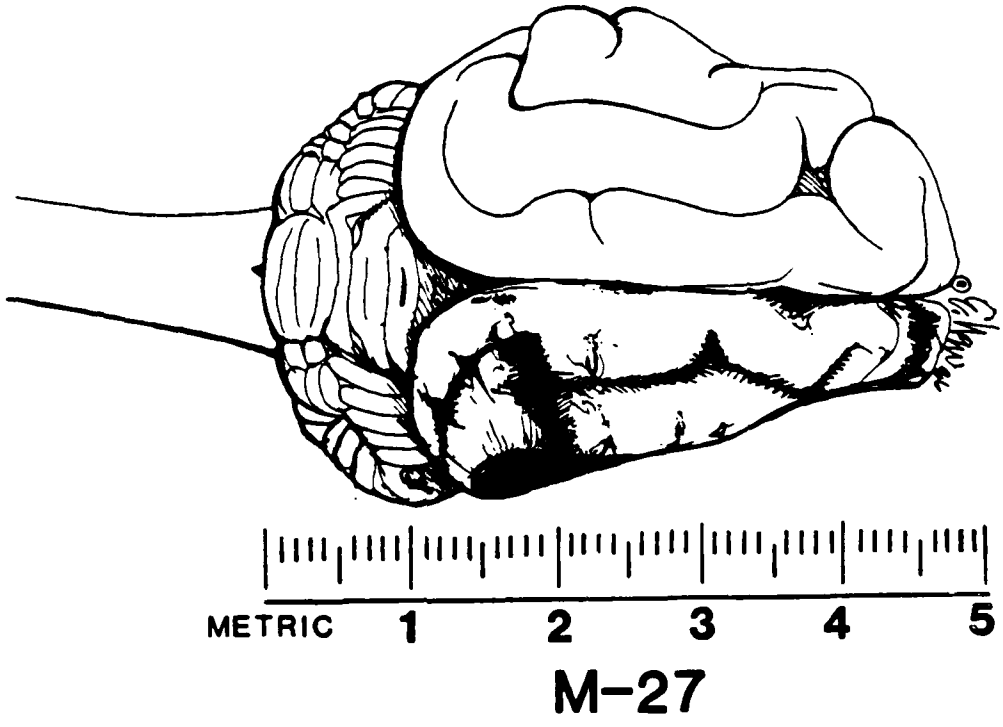


Figure 7: Dorsal view of cat's brain. The frontal lobe entry site is to the right; the end of the missile track (not visible in this projection) is to the left in the occipital-parietal temporal lobe. Missile trajectory slants laterally away from the midline and brainstem.

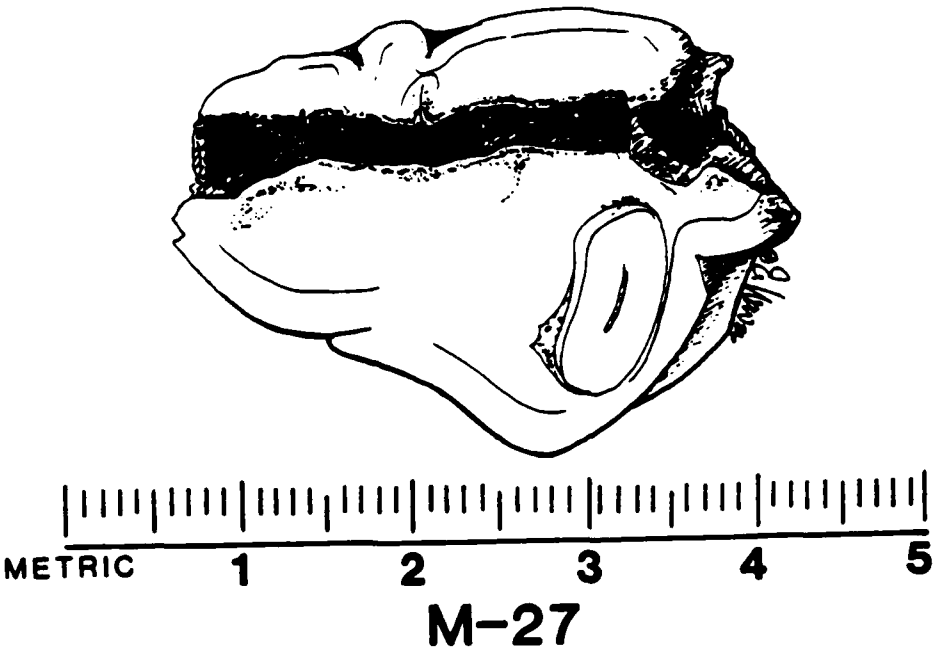


Figure 8: Lateral view of cat's brain. The frontal pole is to the left; the occipital-parietal-temporal lobe is to the right. The missile track extends from the right frontal lobe in the region of the cruciate gyrus through the white matter of the hemisphere to the lateral occipital-parietal-temporal area. This is a line drawing of a fixed specimen demonstrating the permanent missile track.

6. MISSILE ENERGY

Our experiments have shown that from 0.5 to 0.7 Joules of energy are required to effect missile penetration of the posterior wall of the cat's frontal sinus which is about 1mm thick. A wound of 2.4 Joules kills 100% of cats by causing immediate respiratory arrest. Using our model and chosen missile trajectory, we have a relatively narrow spectrum of wound energies by which we can evaluate the brain's response to wounding, figure 3. We have selected 3 wound energies to study this response: 0.9 Joules, the lowest energy which will consistently result in skull and brain penetration; 1.4 Joules, an intermediate energy which, in preliminary tests, resulted in deaths of about 50% of cats and 2.4 Joules, a wound energy which is uniformly fatal.

PHYSIOLOGIC STUDIES

In these initial studies we have investigated the effect of brain wounding on: 1) Respirations; 2) Behavior; 3) General Physiologic Responses; 4) Blood-Brain Barrier; 5) Brain Water and Electrolytes and 6) Cerebrospinal Fluid and Brain Prostaglandins

7. THE EFFECT OF A BRAIN WOUND UPON RESPIRATIONS

1) Central respiratory effects:

Ideally, it would have been most realistic to wound awake and normally functioning cats. Practically, and for humane reasons, this was and is not possible. Because men wounded in combat obviously are breathing spontaneously at the moment of wounding, we decided to wound anesthetized cats which had spontaneous respirations. They were not paralyzed nor placed on a respirator before wounding. Allowing our cats to breathe spontaneously during wounding was more "realistic" but we could not control their blood gases at will as we could have done had we paralyzed the cats and placed them on a respirator.

Because our cats were breathing spontaneously at the time of wounding we quickly realized that higher energy missile wounds had a major effect upon brainstem respiratory centers. The chief cause of death in our cats was the immediate cessation of respirations upon missile impact. For humane reasons and to minimize the cost of this project, we placed all apneac cats on a respirator if they did not breathe after one minute. To our surprise many initially apneac cats resumed spontaneous respirations after respiratory support lasting a few to many minutes. Owing to the end-expiratory CO_2 trace on the physiograph, we could detect the return of spontaneous respiratory effort by the brain-wounded animals. The length of apnea following missile wounding at 0.9 and 1.4 Joules is summarized in tables 1 and 2. These tables also indicate the length of time all wounded cats survived. Some died from their brain wound but most lived (many after being placed temporarily on a respirator) until they were sacrificed.

Table 1: OUTCOME OF 36 CATS WOUNDED WITH A 0.9 JOULE MISSILE

Duration of Apnea (minutes)	No. Cats	Length of Time to Death	Length of Time to Sacrifice
0	5	>36h	6h, 6h, 72h, 72h
through 0.20	6		1h, 1h, 6h, 24h, 24h, 48h
0.21-0.40	7		24h, 48h, 48h, 72h, 72h, 7d, 7d
0.41-0.60	4		24h, 72h, 72h, 7d
0.61-0.80	3		1h, 24h, 72h
0.81-1.00	2	2.5h	1h
>1-<4	4		1h, 1h, 72h, 7d
4-10	3[▲]		>1hr* 72h, 7d
11-20	0		
21-40	1[▲]	21 min**	
41-60	1[▲]		1hr
Total	36		

▲ "Fatal Wounds" by virtue of apnea lasting > 4 minutes.

* Animal ventilated to 4.5 minutes after wounding then began breathing but had further apnea episodes, requiring respirator.

** Animal ventilated from 4-21 minutes after wounding, but could not be further ventilated and had drastically decreased lung compliance with death at 21 minutes (probable neurogenic pulmonary edema).

Table 2: OUTCOME OF 38 CATS WOUNDED WITH A 1.4 JOULE MISSILE

Duration of Apnea (minutes)	No. Cats	Length of Time	
		to Death	to Sacrifice
0	1		24h
through 0.20	3		1h, 1h, 24h
0.21-0.40	6		1h, 24h, 24h, 72h, 7d, 7d
0.41-0.60	6	overnight	6h, 24h, 24h, 24h, 7d
0.61-0.80	2	overnight	48h
0.81-1.00	3	6h	24h, 7d
>1-<4	2		1h, 72h
4-10	4▲	overnight	2h, 24h, 72h
11-20	4▲	20min* 131min	24h, 24h
21-40	3▲	overnight	6h,** 48h
41-60	1▲		1h
61-92	3▲		1.5h, 24h, 21mos
Total	38		

▲ "Fatal wounds" by virtue of apnea lasting > 4 minutes.

* Animal on respirator, but lungs could not be inflated, died at 20 minutes (probable neurogenic pulmonary edema).

** Animal was apneac 24 minutes, then spontaneously breathed 24 to 105 minutes but then became permanently apneac.

Perusal of Tables 1 and 2 shows unequivocally that a 1.4 Joule missile has a significantly more deleterious effect on respirations than does a 0.9 Joule missile.

Though most cats survived their initial apnea assisted by respiratory support, for the purpose of data analysis we consider any cat which had post-wounding apnea of 4 minutes or longer to be "dead", i.e. the animal received a wound which, in the absence of respiratory support after the initial minute, would have proved fatal because of prolonged respiratory arrest. We feel this is quite a valid assumption: a soldier in the field receiving a brain wound which might cause transient apnea would surely die if adequate respiratory resuscitation were not undertaken and respirations restored within the first several minutes of wounding.

Table 3, largely derived from tables 1 and 2, summarizes the outcome of 85 cats wounded in the right cerebral hemisphere. These cats were intended primarily for the study of brain edema or behavior after wounding; intracranial pressures were not measured in these animals. In addition to the large number of cats wounded at 0.9 and 1.4 Joules, table 3 includes 2 cats wounded at 2.4 Joules. Both promptly became permanently apneac. We were initially reluctant to wound many more cats at this high energy out of deference to those who might decry the "needless" sacrifice of animals. Nevertheless the respiratory effects of brain wounding loom so important that we now feel justified in bringing the number of cats wounded at 2.4 Joules up to 9 or 10. This we will do shortly. We also wounded 9 cats in the right cerebral hemisphere with a 2mm rod to see if there were any differences between a 2mm diameter missile injury and a 2mm diameter injury from a rod.

Table 3: OUTCOME FOLLOWING A BRAIN WOUND OF VARIOUS ENERGIES

	Died or Would Have Died Without Respiratory Support	Lived	Total
Rod injury	0	9	9
0.9 Joule missile	5	31	36
1.4 Joule missile	15	23	38
2.4 Joule missile	2	0	2
Total	22	63	85

The rod produced a very low energy, cutting lesion in the brain which had no effect upon the brainstem 1 to 2cm away from the right hemisphere wound. This injury was uniformly non-fatal and it did not cause any respiratory abnormalities. Increasing missile energy from 0.9 to 1.4 to 2.4 Joules markedly increased the numbers of cats which experienced severe central respiratory difficulties immediately after wounding and, thus, increased mortality (as defined by an initial apnea of greater than four minutes). The probability of a 0.9 Joule missile causing a fatal wound from respiratory arrest was 5/36, (0.14) while that of a 1.4 Joule missile was 15/38, (0.39).

Table 4, also largely derived from tables 1 and 2, demonstrates the increasingly severe respiratory disturbances seen with brain wounds of increasing energy.

Table 4: EFFECT UPON RESPIRATIONS BY A RIGHT HEMISPHERE BRAIN WOUND OF INCREASING ENERGY (ANIMALS APNEAC >1 MINUTE PLACED ON RESPIRATOR UNTIL RESPIRATIONS RESUMED; ANIMALS APNEAC >4 MIN CONSIDERED "DEAD")

	% Never Apneac	% Spontaneously Resuming Respirations in < 1 minute	% Spontaneously Resuming Respirations from 1-4 iminutes	% Apneac >4 mins
0.9J(N=36)	13.9	61.1	11.1	13.9
1.4J(N=38)	2.6	52.6	5.2	39.4
2.4J(N=2)	0	0	0	100

Of 36 cats wounded with a 0.9 Joule sphere, 13.9% never had any difficulty with respirations whatsoever and only 13.9% sustained an apnea of 4 minutes or longer. In direct contrast are the 38 cats wounded at 1.4 Joules: only 2.6% of these animals had no apnea while 39.4% of this group had an immediate apnea after wounding lasting 4 minutes or greater. Thus, a cat wounded at 0.9 Joules has approximately a 14% chance of sustaining a fatal respiratory arrest while one wounded at 1.4 Joules has about a 40% chance of dying from respiratory dysfunction, usually "central" in origin.

We may next evaluate the efficacy of immediate respiratory support upon a fatal apneac spell consequent to brain wounding. Among cats wounded at 0.9 Joules, 5 developed immediate apnea lasting 4 minutes or longer (i.e. had "fatal" apnea). All were placed on a respirator after one minute of apnea and two resumed normal respirations after 4 to 10 minutes of respiratory support. These cats then lived up to one week, table 1. When sacrificed at 72 hours to 7 days these cats were alert and were recovering from their left hemiparesis induced by their right cerebral brain wound. Fifteen of 38 cats wounded at 1.4 Joules developed immediate apnea of more than 4 minutes. All were ventilated following one minute of respiratory arrest and 12 subsequently resumed spontaneous respirations. Time on the ventilator for these 12 cats ranged from 5 to 80 minutes with a median time of 20 minutes being required until return of spontaneous respirations. Perusal of table 2 reveals that most of these resuscitated cats lived until time of sacrifice. Again, from 24 hours onward the resuscitated cats were increasingly alert and showed progressive recovery from their cerebral cortical lesions. Their quality of survival was excellent. The effect of immediate respiratory support for the brain-wounded cats is summarized in table 5.

Table 5: MORTALITY OF MISSILE WOUNDS DEPENDING UPON AVAILABILITY OF RESPIRATORY SUPPORT

	Would Have Died Without Respiratory Support		Died Despite Respiratory Support	
	No.	(Percent)	No.	(Percent)
0.9J (N=36)	5	(13.9%)	3	(8.3%)
1.4J (N=38)	15	(39.4%)	3	(7.9%)
2.4J (=2)	2	(100%)	2	(100%)

Clearly, provision of prompt (beginning at 1 minute) respiratory support to cats rendered apneac following brain wounding greatly increased the number of survivors and lowered mortality.

Table 6 indicates the cause of death for the 6 cats which failed to survive despite immediate ventilatory support.

Table 6: CAUSE OF DEATH AMONG ANIMALS DYING OF RESPIRATORY FAILURE AFTER BRAIN WOUNDING

	Immediate, Permanent Central Respiratory Failure	Delayed, Permanent Central Respiratory Failure	Peripheral (Pulmonary) Respiratory Failure	Total
0.9J (3)	2	0	1	3
1.4J (3)	1	1	1	3
Total	3	1	2	6

The predominant cause of death in these brain-wounded cats was immediate, permanent, central respiratory failure. As the missile wound was in the cerebral hemisphere, effects upon the brainstem must have been indirect. Presumably, hydrostatic overpressure caused by the missile or the shock wave associated with missile passage affected brainstem respiratory centers which were 1 - 2cm away from the actual missile track.

Knowing the exact meaning of the single case of delayed, permanent central respiratory failure is difficult. While this may represent a primary brainstem phenomenon affecting respiratory centers in a delayed fashion, the apnea might also have been from medullary compression caused by intracranial bleeding.

Interestingly enough, two of the six fatalities following brain wounding occurred from lung failure as these animals absolutely could not be ventilated following their brain wound. Their lungs became totally noncompliant and the cats could not be oxygenated; we assume that they developed neurogenic pulmonary edema.

CLINICAL SIGNIFICANCE OF THE EFFECT OF MISSILE WOUNDING UPON RESPIRATIONS

Our experiments strongly suggest that integrity of brainstem function, and specifically central respiratory drive mechanisms located in the brainstem, most often determine whether the individual lives or dies after a low velocity missile wound of the cerebral hemisphere. Missile injury to the brain may kill, not from innately fatal brain damage per se but from an associated respiratory arrest. Our experiments have also shown that this respiratory arrest may be reversible if ventilatory support is given within one minute after brain wounding.

The transient disturbance in respiratory drive following a missile wound to the cerebral hemispheres may be likened to a respiratory "concussion". Just as head injury may cause temporary loss of consciousness (concussion) from disturbance of the reticular activating system (RAS) (6) so, too, may the missile injury cause a temporary cessation of respirations. With transient injury to the RAS alone the person becomes unconscious but respirations continue. As the RAS recovers the person awakens. Indirect missile injury to central respiratory drive mechanisms may result in brainstem disturbance and a temporary cessation of respirations. If the respiratory arrest is mild so that respirations will resume in a minute or so the brain-wounded person may well recover. If the respiratory arrest lasts longer than several minutes the individual will die, not from an inherently fatal brain injury but from a superimposed (and often potentially reversible) failure of medullary respiratory centers.

Our experiments have demonstrated that if timely ventilatory support were given more than 80% of brain-wounded animals rendered initially apneac for longer than one minute recovered their innate respiratory drive (7/9 of 0.9 Joule-wounded cats, table 1; 14/17 of 1.4 Joule-wounded cats, table 2).

Among the 9 resuscitated 0.9 Joule-wounded cats 7 survived until sacrifice. Four of these were euthanized 3 to 7 days after wounding and resuscitation. Seventeen cats wounded at 1.4 Joules required temporary ventilatory support and 14 survived until sacrifice. Eight lived from one day to 21 months following their brain wound. The neurologic quality of surviving cats that had been temporarily apneac and required respiratory support was no different from cats which did not sustain protracted apnea after wounding. One cat resumed spontaneous respirations after 75 minutes on the respirator and lived for 21 months as an apparently normal cat! It is quite likely, therefore, that many brain-wounded soldiers rendered apneac by a missile fragment to a cerebral hemisphere could be saved if early ventilatory support were administered. This could probably be done by mouth to mouth resuscitation from a corpsman or other soldier.

Our experiments also indicate that the neurologic quality of life among those cats which received timely respiratory resuscitation was no different than those animals which never needed respiratory support. Thus, no reason exists to suspect that humans rendered temporarily apneac by a missile wound to the brain would not, upon resuscitation, have as good a quality of life as those with brain wounds who were not made apneac.

While most apneac cats which required respiratory support recovered spontaneous respirations, 3 did not and we do not know the reason why. The pathophysiology of irreversible apnea remains unknown; whether it is mechanical, biochemical, vascular or a combination of all three. Since we do not know the pathophysiological substrate of "irreversible" apnea we do not know whether or how it may be treated and reversed. Clearly, further research is needed in this area. The effects of missile wounding upon respirations are summarized in figure 9.

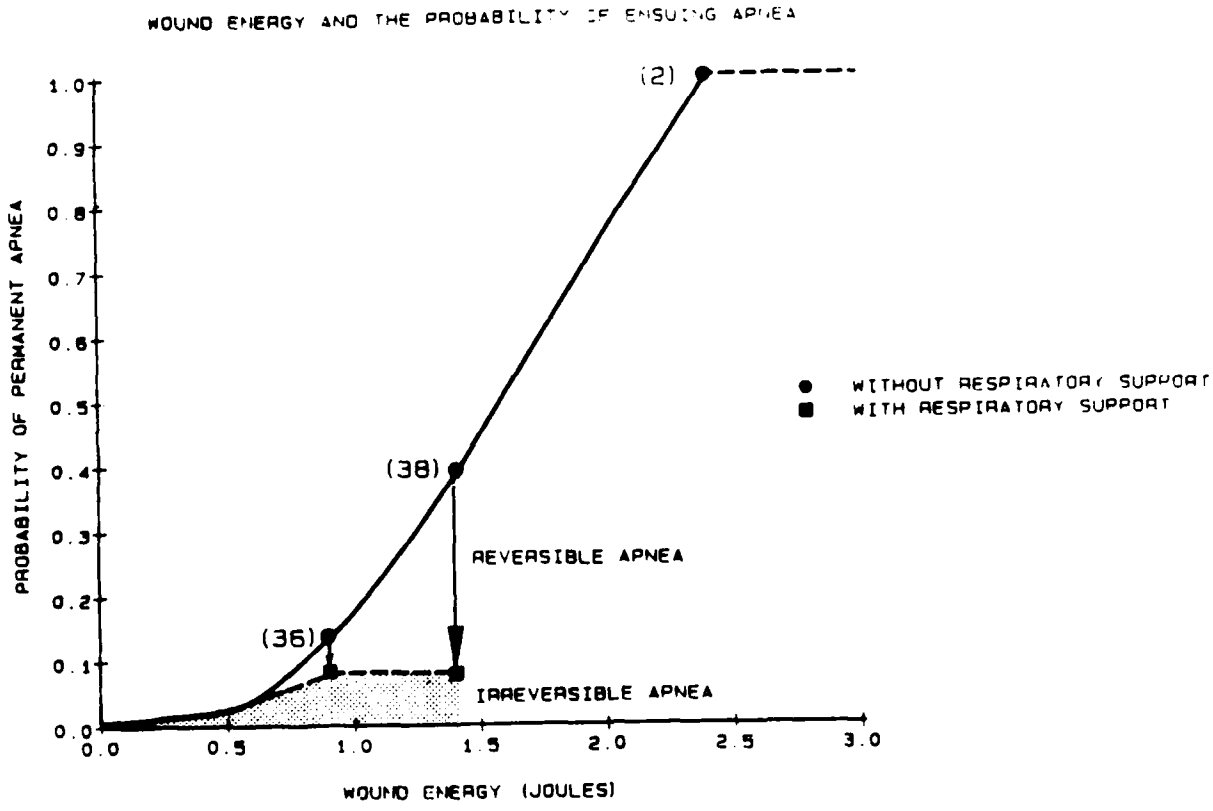


Figure 9: Cats wounded at 0.9 Joules had about a 14% chance of fatal apnea while those wounded at 1.4 Joules had about a 40% chance fatal respiratory arrest (top solid line). With respiratory support, however, only about 8% of cats wounded at either energy remained permanently apneac. At both 0.9 and 1.4 Joules wounding energy more than 90% of animals had transient, reversible medullary dysfunction. When the wound energy was increased to 2.4 Joules damage to medullary respiratory centers became irreversible and permanent.

Since we have already worked out the spectrum of respiratory disturbances to be expected after 0.9, and 1.4 Joule missile injuries, figures 10 and 11, modification of these patterns by pretreatment with various drugs (e.g. cholinergic blockers) may indicate mechanisms of brainstem dysfunction following wounding and whether specific drugs might be effective in modifying missile-induced apnea.

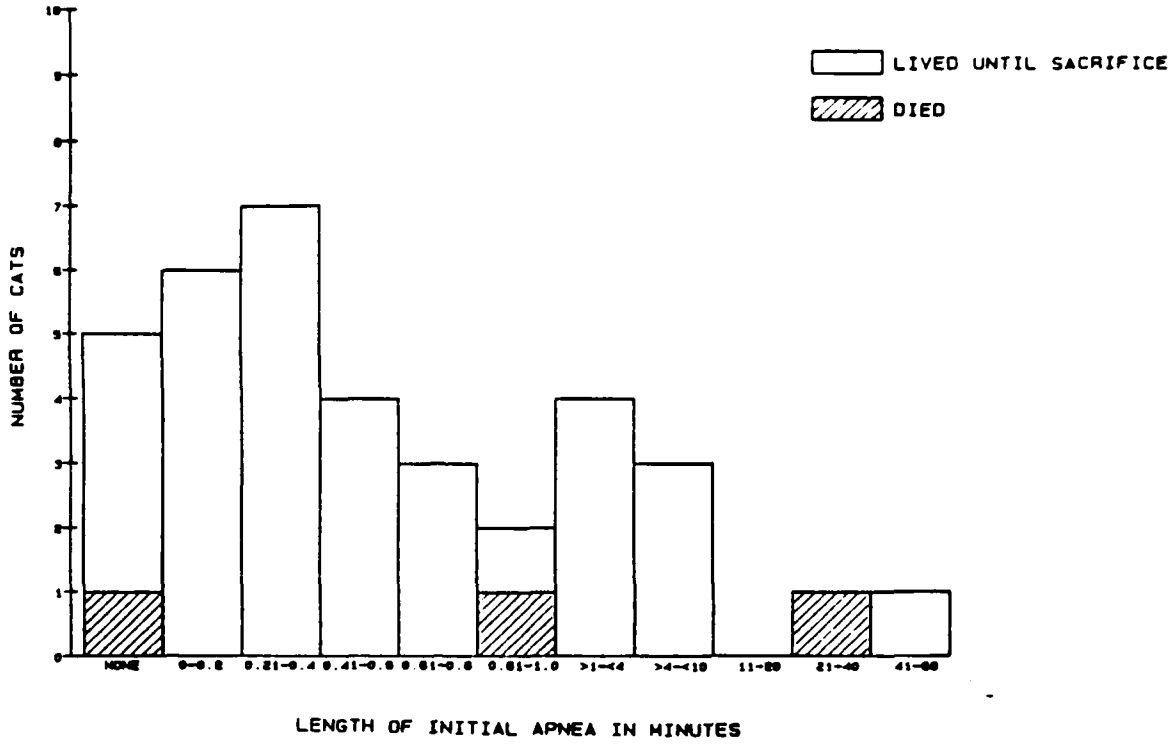


Figure 10: Spectrum of respiratory disturbances seen among 36 cats wounded at 0.9 Joules (from table 1). Length of time of initial apneac period (in minutes) is plotted on x-axis. Number of cats in each apnea period is indicated on the y-axis.

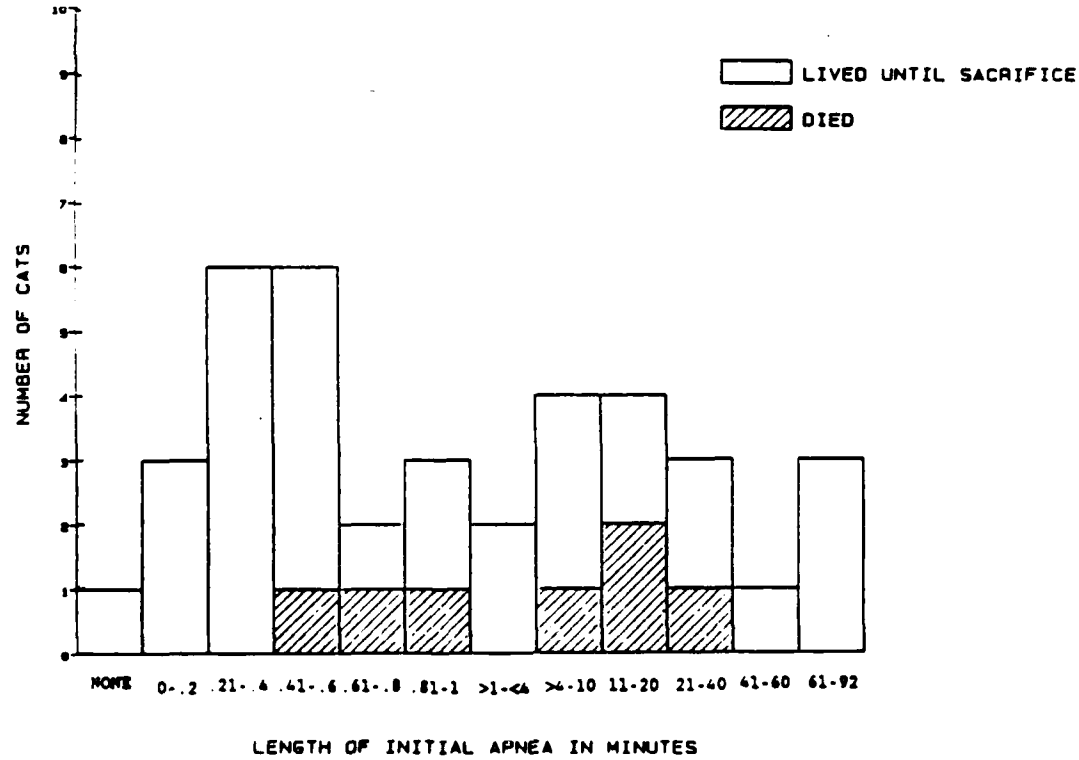


Figure 11: Spectrum of respiratory disturbances seen among 38 cats wounded at 1.4 Joules (from table 2). Length of time of initial apneac period (in minutes) is plotted on the x-axis. Number of cats in each apneac period is indicated on the y-axis.

The respiratory effects of brain wounding which we have observed are so striking that one may ask whether this is a general effect or is unique to our model, chosen anesthetic (pentabarbital), and wound trajectory. In the future we will alter the wound trajectory and anesthesia to see whether apnea is still a prominent effect. If so, it would be important to study this problem in great detail in primate brains because the configuration of primate brains is more akin to the human. If respiratory arrest following brain wounding proved to be significant in brain-wounded primates then the Army should consider the practicality and feasibility of administering immediate respiratory support to those receiving a brain wound in combat. The means of providing this support will have to be worked out (mouth to mouth respirations, phrenic nerve stimulators, direct respiratory center stimulation or other means). Tiding over those who have sustained a brain wound and concomitant "respiratory concussion" until the innate respiratory drive mechanisms return may significantly lower the mortality of brain wounds in combat.

2) Peripheral Respiratory Effects:

Our experiments have clearly shown that a missile wound to the brain may affect the lung: 2 of 76 missile-wounded cats died from fulminant lung failure and probable neurogenic pulmonary edema. Phenomena affecting lung function after brain wounding will be discussed more fully in the section on PHYSIOLOGIC MONITORING, Section 9.

8. BEHAVIOR AFTER WOUNDING

In addition to studying the acute physiologic effects of missile wounding we felt it would be important to ascertain the behavioral and neurologic recovery pattern of cats following our standard right hemisphere brain wound. Once having established the "normal" recovery pattern following wounding we would be in an excellent position to see whether drug therapy would significantly modify neurologic recovery. Drugs which speed up recovery of neurologic function following brain wounding would be excellent candidates to study in detail to learn their mechanisms of action and to see whether they might be of use in humans with brain wounds. To our knowledge we are the first study group to evaluate animal behavior following recovery from a penetrating brain wound.

In this pilot study on post wounding behavior we evaluated and scored four groups of cats:

5 control cats:	These cats underwent all anesthetic and surgical procedures but were not wounded.
5 rod-injured cats:	These cats underwent all anesthetic and surgical procedures and were wounded in the right hemisphere by a 2mm rod.
10 missile-wounded cats:	These cats underwent all anesthetic and surgical procedures and received a right cerebral hemisphere wound of either 0.9 Joules (5 cats) or 1.4 Joules (5 cats).

The cats were wounded only when fully anesthetized and, hence, did not feel any pain. Local anesthetic skin ointment was applied to all incisions of surviving cats to prevent postoperative pain but no other analgesic drugs were given during the post wounding recovery phase to avoid interfering with the cats' natural behavior after wounding. No cat appeared in pain at any time during these intervals.

Animals surviving their wound were scored for several days on the following neurologic and behavioral tests:

(A) Neurological Response

Motor function	Score
Cat walks with normal gait-no neurological deficit	6
Cat walks with abnormal gait, has mild hemiparesis	5
Cat barely walks with moderate hemiparesis	4
Cat unable to walk with moderate hemiparesis	3
Cat unable to walk with severe hemiparesis	2
Cat unable to walk with hemiplegia	1
Sensory function	
Cat responds appropriately to tactile and noxious stimuli (paw pinch)	5
Cat responds appropriately to noxious limb stimuli only	4
Inappropriate response to noxious limb stimulation	3
Reflex response to noxious limb stimulation	2
No response to noxious limb stimulation	1
Level of consciousness	
Awake and alert	5
Awake and alert with lack of spontaneous movements	4
Drowsy, responds only to noxious stimuli	3
Stuporous, minimal response to noxious stimuli	2
Comatose	1

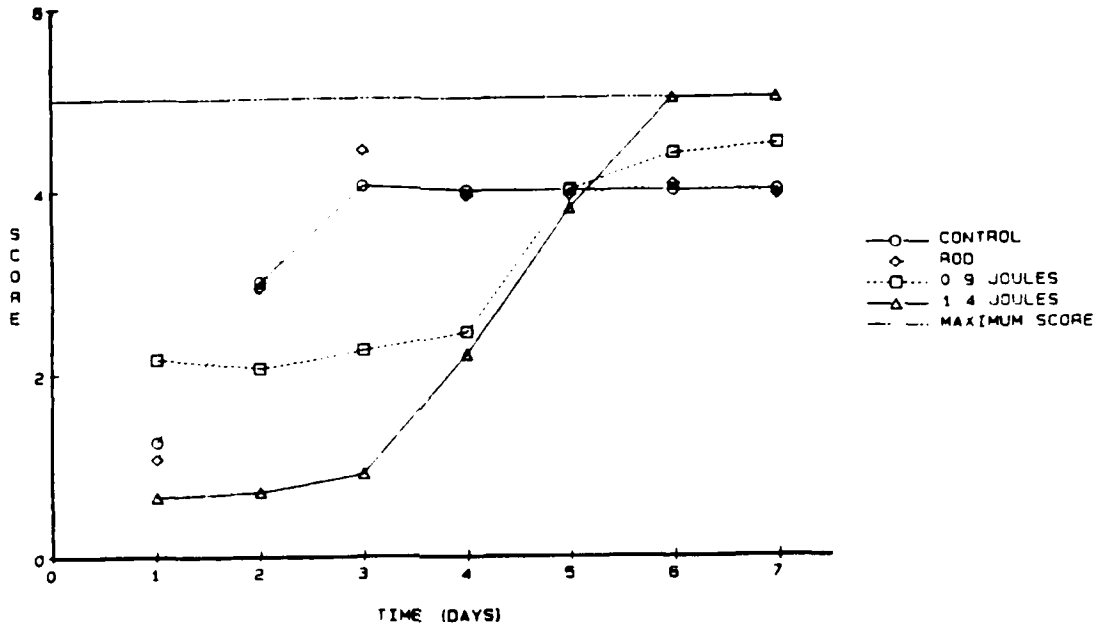
(B) Spontaneous Food and Water Intake: Lactated Ringer's solution was injected subcutaneously to provide adequate daily fluid maintenance until cats began to eat and drink voluntarily. Spontaneous water and food intake was scored:

(a) Water intake; 1/4 point for each 4cc per day of water intake (or part thereof) up to a maximum of 5 points

(b) Food intake; 1/4 point for each 4g per day of food (or part thereof) up to a maximum of 5 points

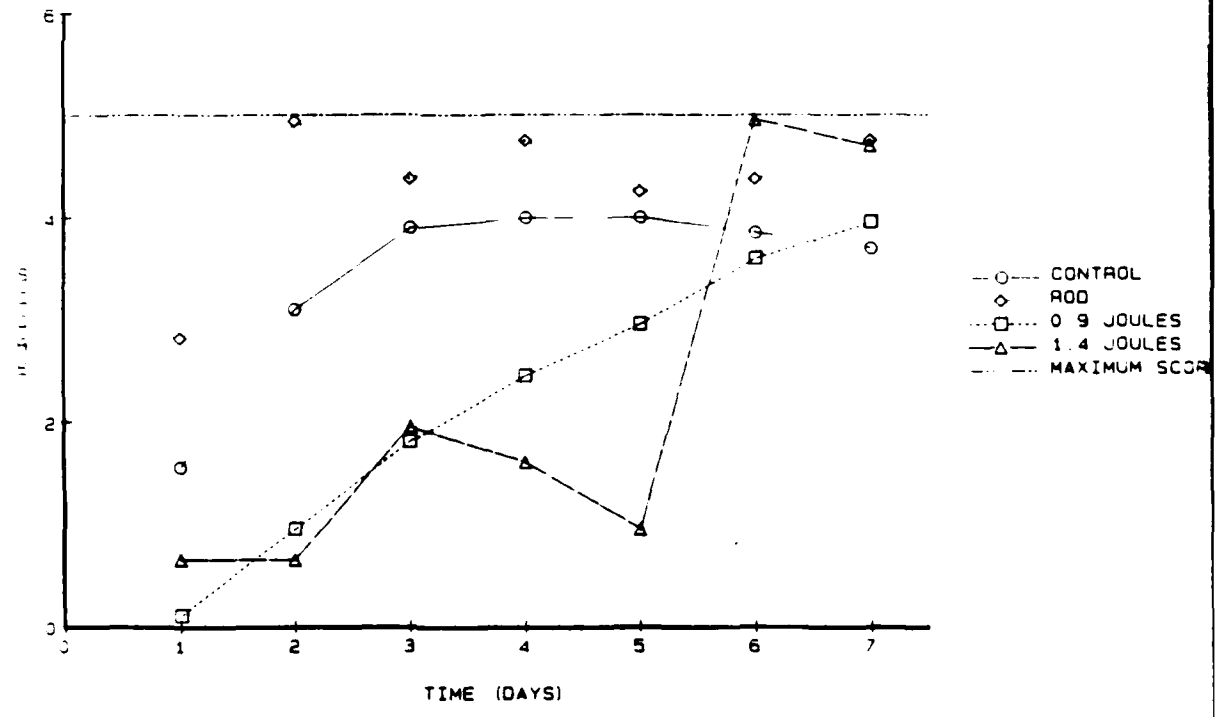
(C) Composite Score: This was the sum of A and B above, the maximum being 26 points.

All scored behavioral and neurologic data are presented in figures 12 to 17.



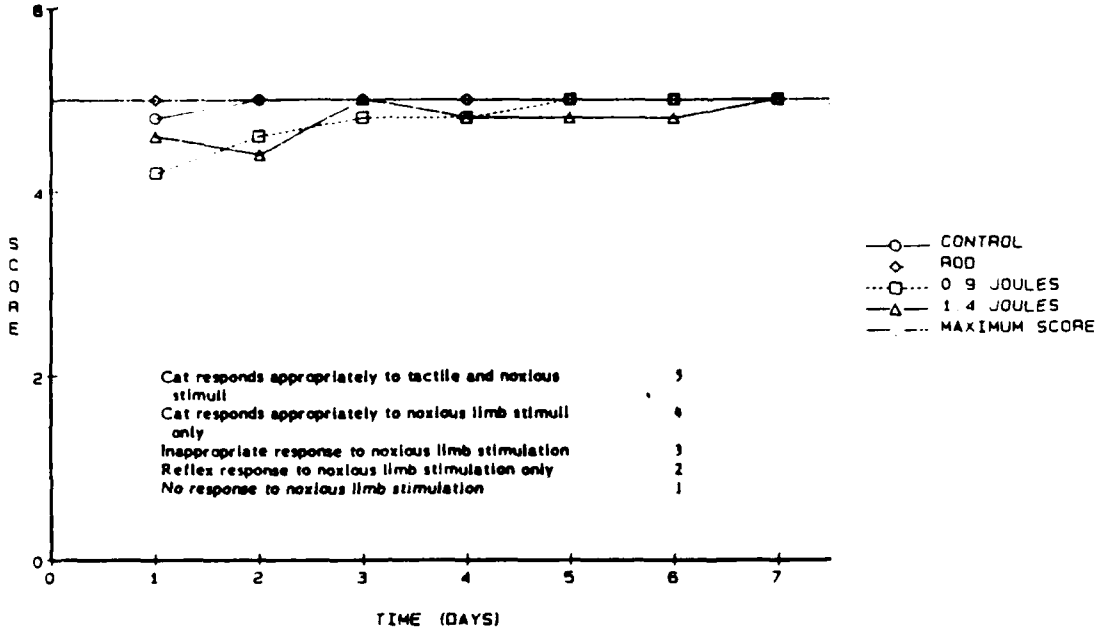
Values are means (n=4-5). Maximum score=5

Figure 12: Water consumption following wounding.



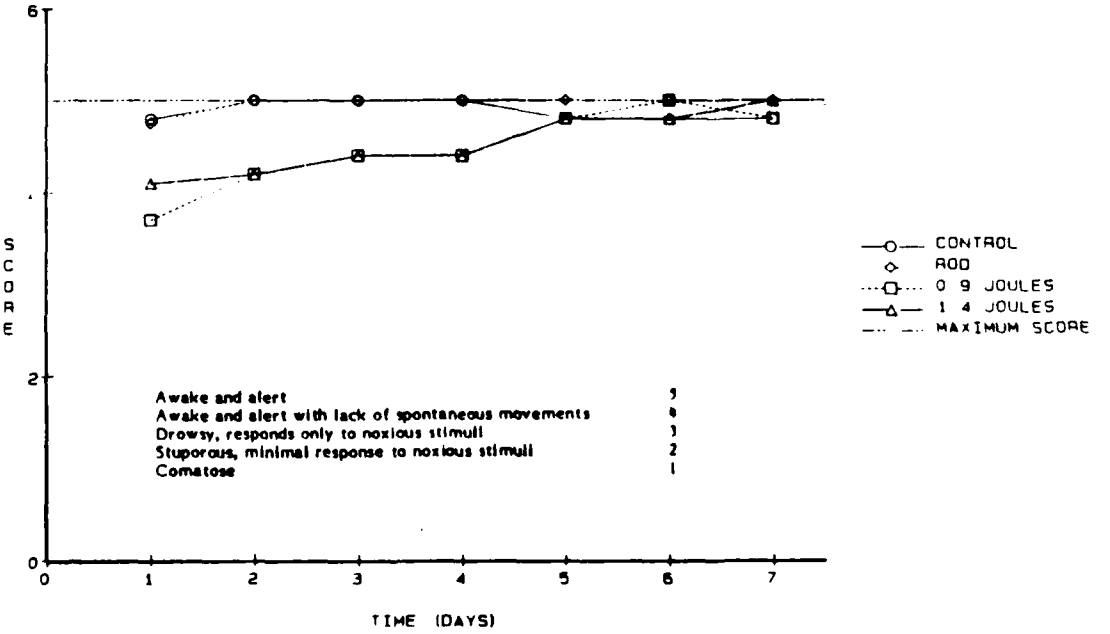
Values are means (n=4-5). Maximum score=5.

Figure 13: Food consumption following wounding.



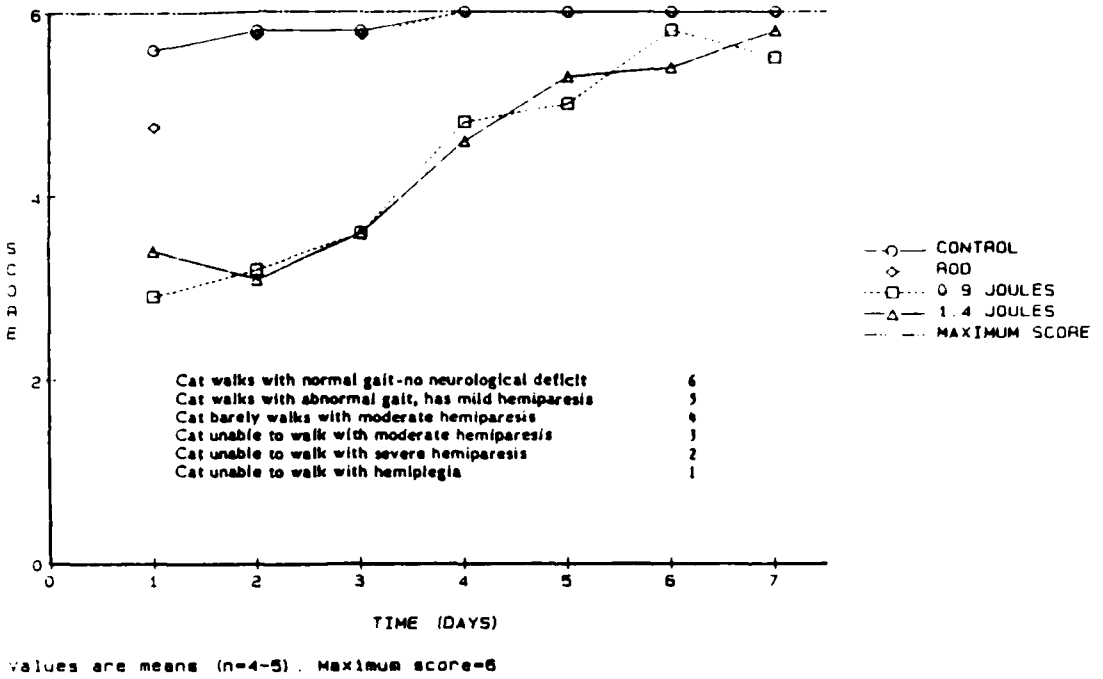
Values are means (n=4-5). Maximum score=5.

Figure 14: Response to pain following wounding.



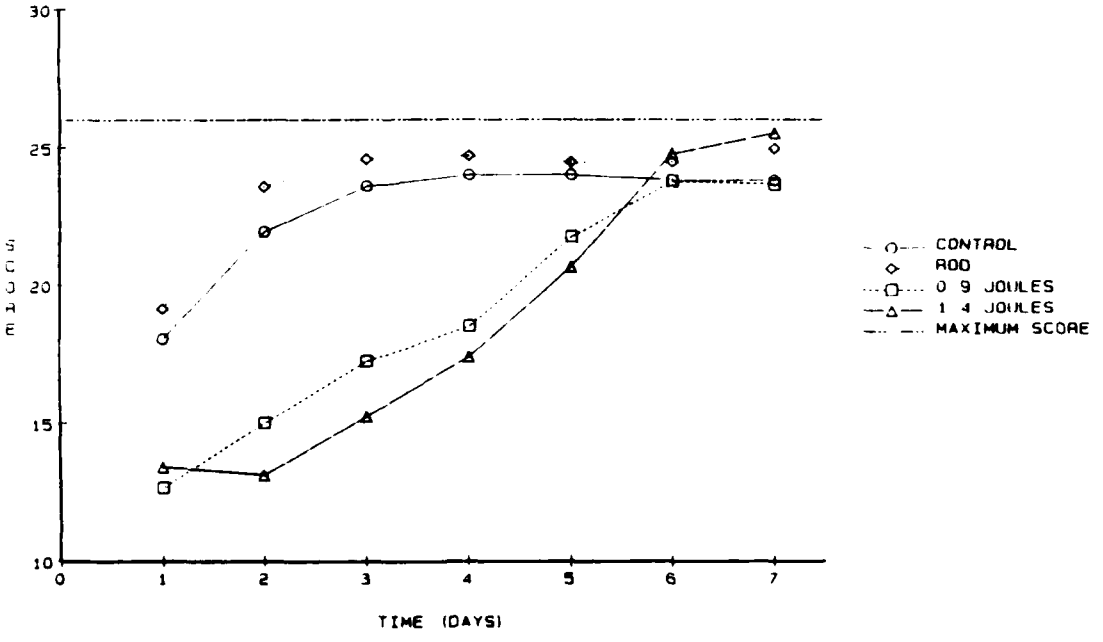
Values are means (n=4-5) Maximum score=5.

Figure 15: Level of consciousness following wounding.



Values are means (n=4-5). Maximum score=6

Figure 16: Motor function following wounding.



Values are means (N=4-5). Maximum score=26

Figure 17: Composite behavioral score following wounding.

DISCUSSION

Previous studies from other laboratories have only considered the acute physiological changes that occur within the first few hours of a brain wound.(7-15) We have successfully created an animal model which enables the study of pathophysiological and neurochemical mechanisms for weeks to months following a missile wound to the brain. We can begin to make correlations between the neurologic status of the missile-wounded animal and the underlying neurochemical changes within the brain caused by the missile.

The low energy (cutting) rod injury produced no appreciable neurologic deficit. This result is consistent with the rod injury not causing any appreciable blood-brain barrier breakdown or cerebral edema, (see BLOOD-BRAIN BARRIER, Section 10 and BRAIN EDEMA, Section 11).

We have shown that the 0.9 and 1.4 Joule missile wounds produce markedly different effects upon medullary respiratory centers: the 1.4 Joule missile wound was much more likely to produce transient apnea than the 0.9 Joule wound. In contrast to this, cerebral cortical dysfunction, evaluated by neurologic and behavioral tests, appeared essentially similar after a wound of either energy, figure 17. The clear differences between wounds of lower and higher energy upon respiratory function and the lack of any such differences upon cortical function indicate that in analyzing a missile's effect upon the brain one has to consider two separate structures: the brainstem and the cerebral cortex. Brainstem dysfunction after missile wounding determines whether the brain-wounded individual will live or die. Cortical damage after wounding will determine the extent of the neurologic residua among survivors.

In our future experiments return of brainstem function following wounding will be noted acutely by return of spontaneous respirations. Return of cortical function (along with supporting subcortical structures as basal ganglia/thalamus) will be measured over days after wounding by means of the various behavioral tests.

Our pilot studies on post wounding behavior showed that missile-wounded cats regained almost normal levels of cortical (and subcortical) function after 5 days. This recovery of neurologic function in the brain-wounded animal is quite analagous to the human situation. Men receiving a brain wound in combat tended to show neurologic improvement and behavioral recovery in the months following their wound.(16) Evidently the cat brain, being "simpler" than the human brain (no corticospinal tract, for instance), may recover from a brain wound more rapidly than a human. This rapid, natural recovery of the brain-wounded cat poses a problem for evaluation of drugs which might enhance neurologic recovery: if the cat recovers by itself in 5 days how will it be possible to see whether a drug provides any benefit? At best we will have but a small "window" to try and determine a drug action upon neurologic recovery of the brain-wounded animal. We are following two strategies to enlarge this "window": 1) Pentabarbital anesthesia depressed behavior in even unwounded cats for about 1-2 days, figure 17. We, therefore, are investigating the possible use of short acting anesthetics as isoflurane for future behavioral experiments. We will then be able to assess cat behavior within a few minutes of wounding. (In some pilot studies we have performed, control cats were fully awake 7 minutes after cessation of isoflurane anesthesia; brain wounded animals were awake within 30 minutes).

2) Perusal of behavioral scores indicates that motor function (including the ability to drink and eat) provided the best indicator of return of cortical function after wounding. In the future we will try to magnify motor deficits by using a balance beam walking test to enhance evidence of residual walking motor deficits. This should increase the length of time motor defects are apparent and the time which we will have to evaluate drug actions.

In addition to the recorded neurologic/behavioral deficits we also observed that many of our brain-wounded cats exhibited turning movements to the right (wounded) side. The abnormal posture of the wounded cats is shown in figure 18 Turning movements have been observed in other experimental situations when ipsilateral caudate dopamine has been deplete 17,18,19. Possibly, the right hemispheral brain wound causes dopamine depletion in the right caudate nucleus. If so, this would be an another example of brain damage at a distance from the missile track. Future studies will investigate the dopamineric system in the caudate nucleus after missile injury.

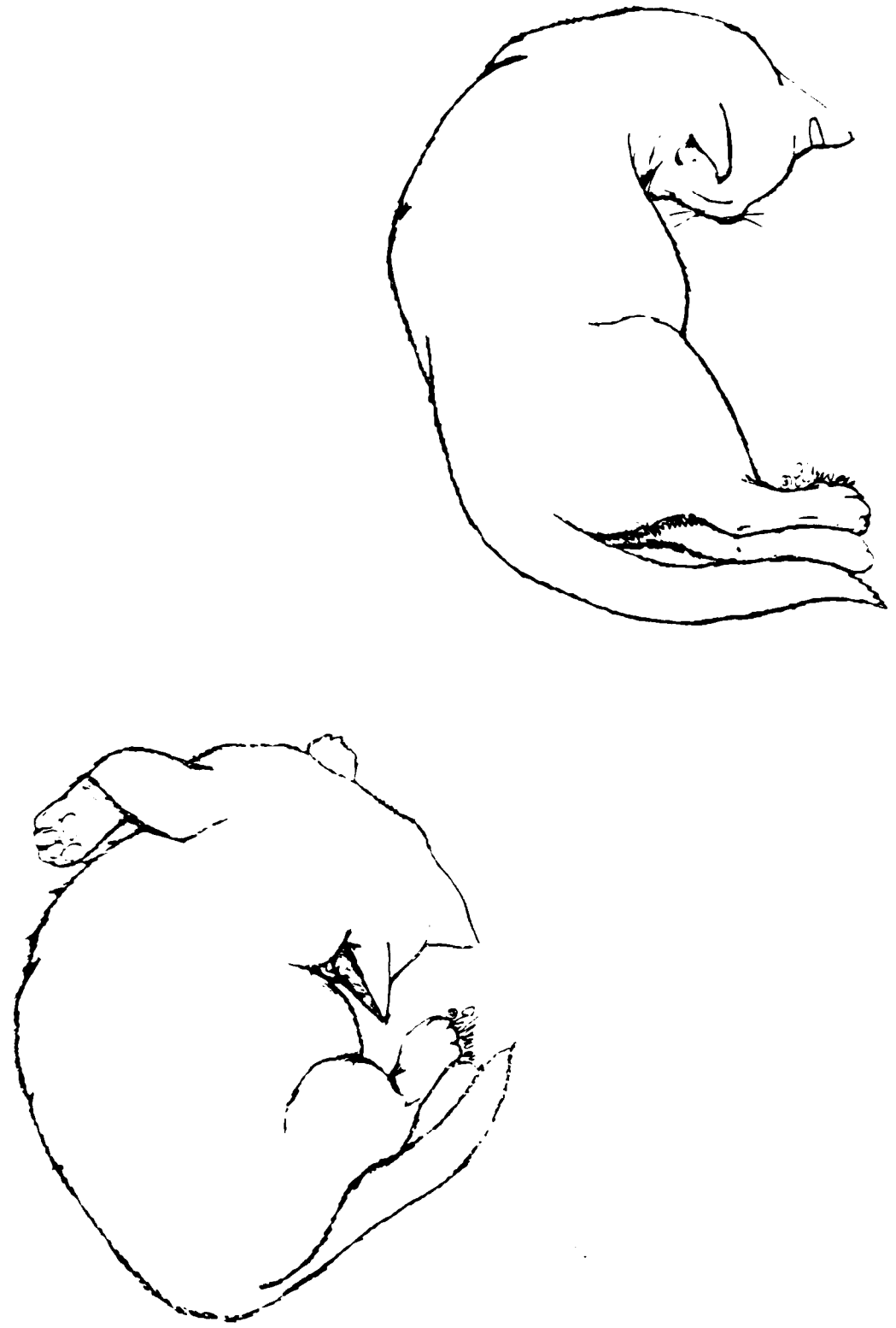


Figure 18: Abnormal posture of cats wounded in the right cerebral hemisphere. Even at rest animals tend to turn to the right. In lower picture abnormal position of paretic left forepaw is evident. (Line drawing from photographs).

9. PHYSIOLOGICAL MONITORING

We instrumented 20 cats to evaluate several physiologic variables after wounding. Five cats were control animals. We wounded three groups of cats at either 0.9, 1.4 or 2.4 Joules. Each of these groups contained 5 cats. All animals had indwelling arterial catheters for continual blood pressure and pulse monitoring plus intermittent arterial blood gas determinations. Respirations were continually recorded by the end-tidal CO_2 trace on the physiograph. We determined intracranial pressure continually by an epidural pressure sensor placed over the left parietal-occipital area.

We recorded the following physiologic variables: mean arterial pressure(MAP), intracranial pressure(ICP), heart rate, respiratory rate, arterial pO_2, pCO_2 and pH plus arterial blood glucose and hematocrit. Cerebral perfusion pressure (CPP) was calculated from the MAP minus the ICP. The variables were recorded during a control period, (the end of which is designated point 0, on tables and figures) and subsequently at 1, 3, 5, 10, 30, 60, 120, 180, 240, 300 and 360 minutes after wounding. These data are presented in tables and graphs in this PHYSIOLOGICAL MONITORING section and also in the APPENDIX, tables 19 through 62, figures 44 through 86. All physiologic data are summarized in tables 19-22.

Though all 20 cats in which we monitored multiple physiologic variables lived 6 hours, we regard only the first post wounding hour to reflect the result of anesthesia plus a brain wound alone. After this, both wounded and control cats began to awaken from anesthesia. This tended to increase intracranial pressure and heart rate and to decrease pCO_2, even in control cats figures 19, 20, 21, 24. Blood glucose tended to increase after this time as well indicating stress-induced gluconeogenesis, figure 22.

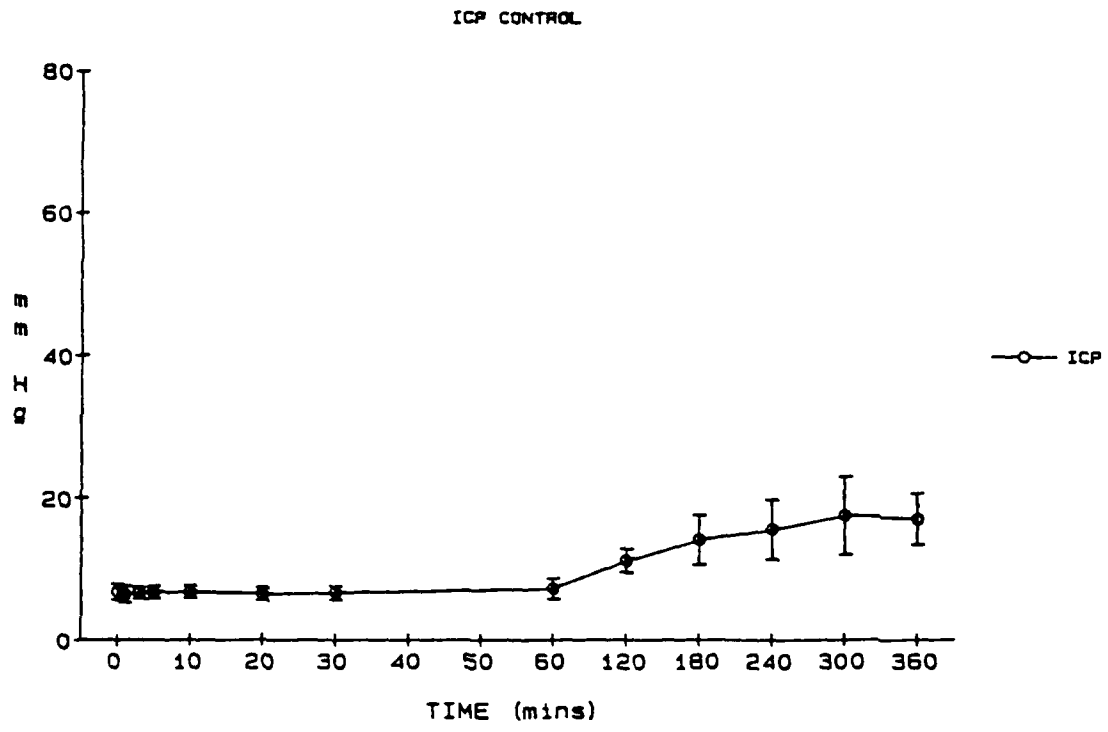


Figure 19: Intracranial pressure in control cats. The rise after one hour of observation occurred because the animals were awakening and tended to strain.

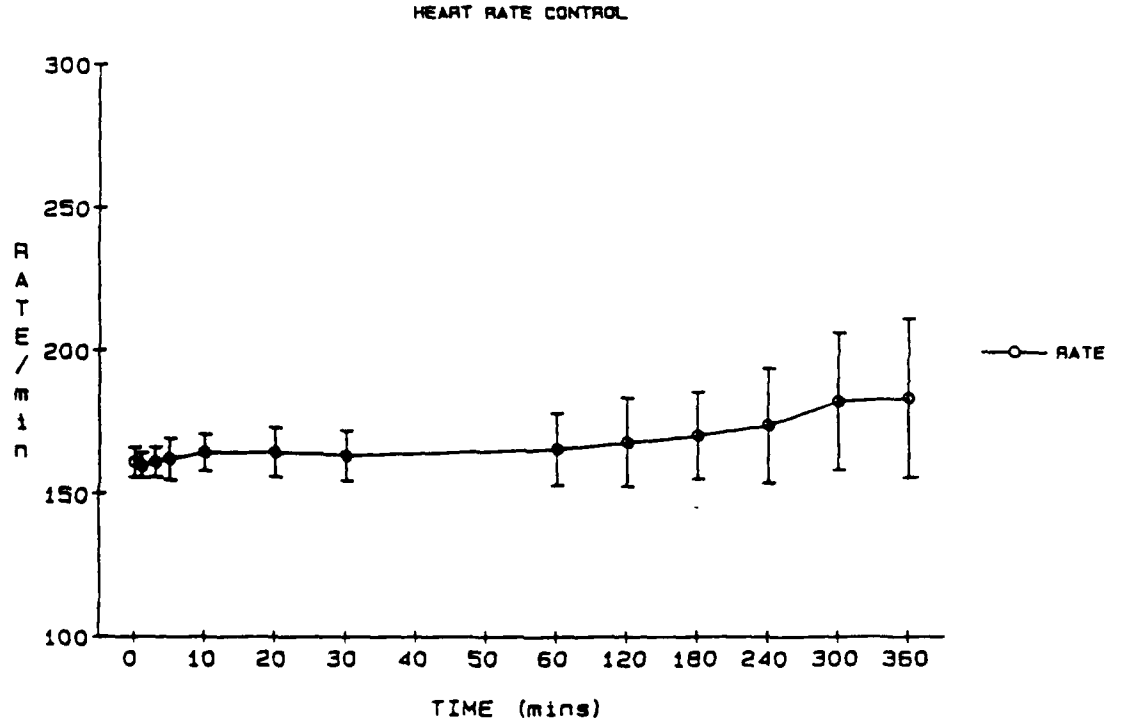


Figure 20: Heart rate in control cats. The rise after one hour of observation occurred as anesthesia wore off, the animals became more alert, and began to be more active.

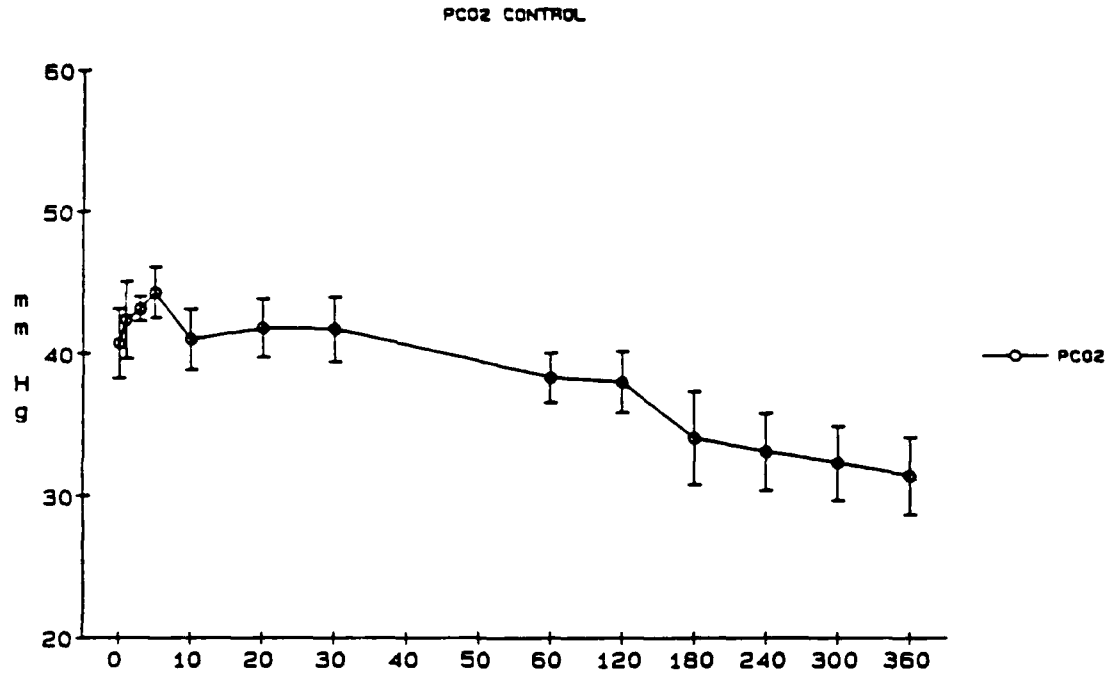


Figure 21: Arterial pCO_2 in control cats. The decrease after one hour of observation occurred as anesthesia wore off, the animals began to be more active, and began to hyperventilate.

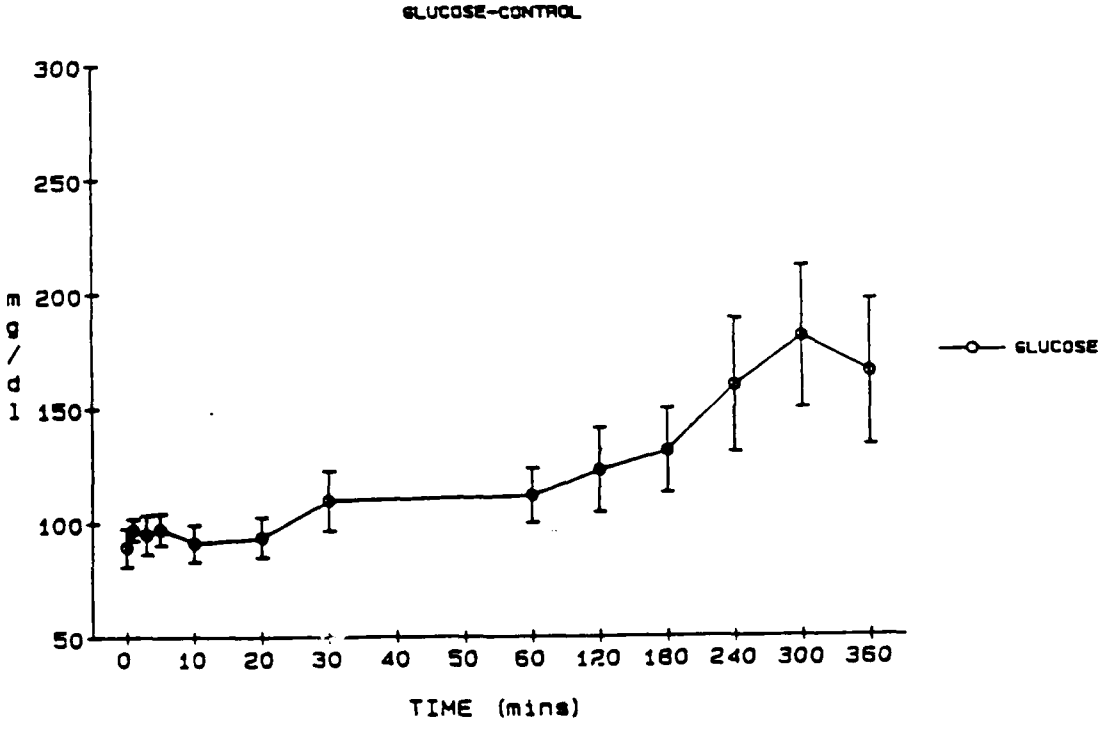


Figure 22: Arterial blood glucose in control cats increased after one hour of observation owing to stress-induced gluconeogenesis.

For purposes of analysis the measured physiologic variables will be grouped into 4 distinct but related groups reflecting:

A. Medullary Function
   1) apneac response
   2) respirations
   3) blood pressure
   4) pulse rate

B. Intracranial Pressure and Cerebral Perfusion Pressure

C. Pulmonary Function
   1) arterial blood gases

D. Systemic Effects
   1) arterial blood glucose
   2) arterial hematocrit

A. Medullary Function

The missile wound to the right cerebral hemisphere wound was often associated with altered respirations, blood pressure and pulse rate. These medullary effects occurred even though the medulla lies 1 to 2cm from the missile path in the cerebrum.

1) Apneac Response

The apneac response following a missile wound to the right cerebral hemisphere has been fully discussed in Section 7. Those data were obtained from cats which were not monitored for ICP; their skulls were fully intact prior to wounding. Monitoring ICP with an epidural balloon catheter modified the apneac response considerably. Table 7 shows the effects of the right cerebral hemisphere wound on respirations for cats without a balloon epidural ICP monitor in place and with such a monitor inserted. Data for unmonitored cats were derived from Tables 1 and 2 while data for the 10 monitored cats came from the experiments specifically designed to evaluate multiple physiologic variables.

Table 7: PERCENT OF CATS EXHIBITING DIFFERENT AMOUNTS OF APNEA AFTER WOUNDING WITHOUT AND WITH AN EPIDURAL PRESSURE MONITOR IN PLACE

	Apnea Pattern Without ICP Monitor		Apnea Pattern With ICP Monitor	
Length of Apnea (Min)	0.9J (36)	1.4J (38)	0.9J (5)	1.4J (5)
None	13.9%	2.6%	20%	0
to 1.0	61.1%	52.7%	80%	60%
1.0-4.0	11.1%	5.3%	-	40%
>4.0	13.9%	39.4%	-	-

( ) Number of cats

Clearly use of the small epidural balloon monitor decreases the liklihood that the right hemisphere brain wound will cause a prolonged apneac response. While almost 40% of cats wounded at 1.4J without ICP monitoring sustained apnea greater than 4 minutes, only 2 ICP-monitored cats exhibited apnea for more than one minute (and only for 61 and 65 seconds respectively: 1.02 and 1.08 min). Possible reasons for attenuation of prolonged apnea with monitoring include trephination (even though the skull hole was sealed with dental acrylic) and the volume of the air-filled monitor itself. The few mm^3 of air within the balloon may be enough to absorb some of the missile energy and, so, to protect the brainstem.

Two significant points arise from these findings: 1) Brain wounds have been made through skull trephine openings in several prior experimental studies.(7-15) Quite possibly brain or somatic dysfunction seen in these studies was quite modified because of the trephine openings which might have greatly attenuated missile energy. 2) If a balloon epidural cannula is used to measure ICP following wounding, higher missile energies will have to be utilized to achieve the same pathophysiologic effects that a lower energy missiles would achieve if fired through a perfectly intact skull. In studying the apneac response in detail we shall have to use higher wounding energies to achieve apnea greater than four minutes if we monitor ICP sinultaneously.

2,3,4) Respiratory Rate, Blood Pressure, Pulse Rate:

In wounded cats respiratory changes usually occurred at the instant of missile impact while hypertension and bradycardia began from 1.5 to many seconds later. Alterations in these physiologic variables controlled by the medulla and the times of their maximum changes after wounding are given in table 8. Following these maximal changes, respirations, pulse rate and blood pressure usually tended to return to their normal range. Complete data on these variables are in Appendix Tables 23-26 and 35-42 and figures 44-48 and 59-66. Blood pressure responses are shown in figure 23.

Table 8: CHANGES IN RESPIRATIONS, BLOOD PRESSURE AND HEART RATE AFTER A MISSILE WOUND TO THE BRAIN
(rates and blood pressure: X ± SD)

Missile Energy	Respiratory Rate		Blood Pressure		Pulse Rate	
	control (rate)	% change at 1 min	control (mmHg)	% change at 1 min	control (rate)	% change at 3min
control	14±4	-8	97±10	+3	161±12	0
0.9	14±4	-36	111±25	+50	196±16	-11
1.4	15±7	-56	108±9	+43	170±13	-10
2.4	13±2	-31	112±18	+53	180±18	-15

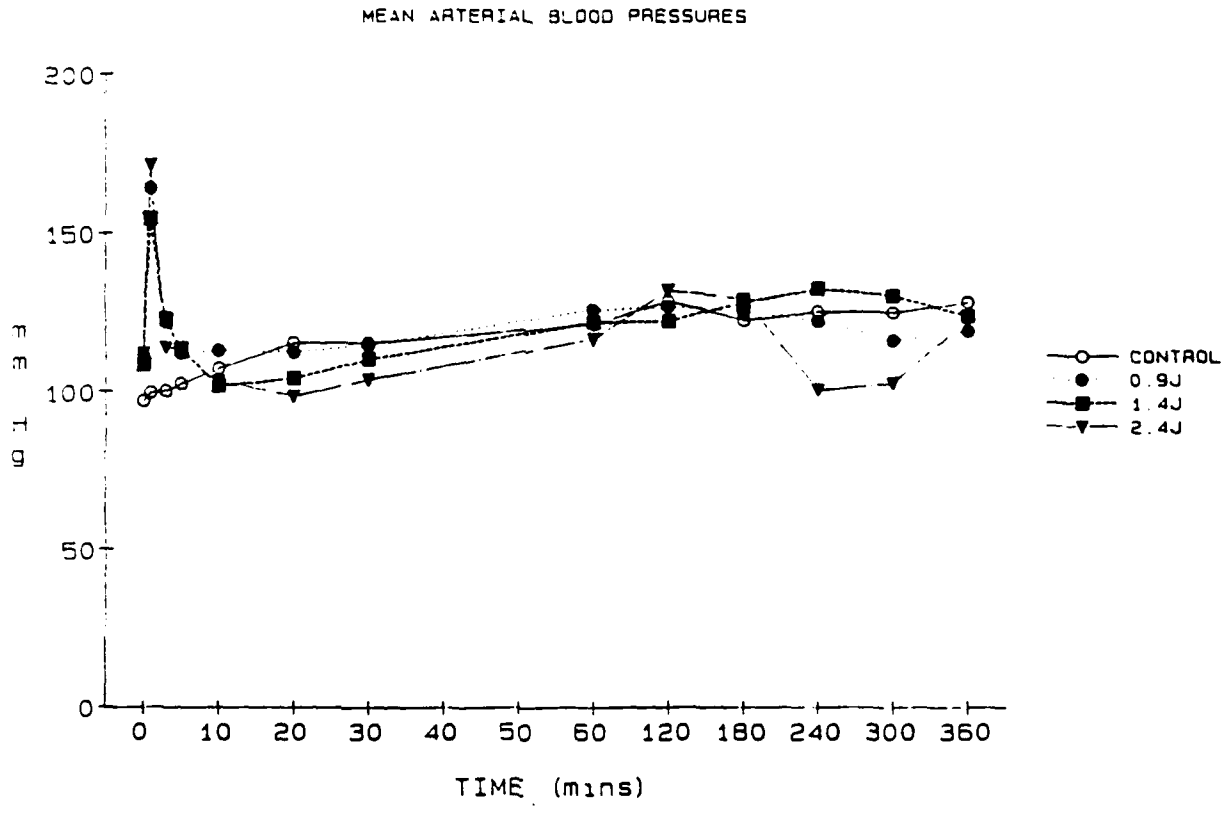


Figure 23: Arterial blood pressure after wounding. Within a few seconds of wounding systemic arterial pressure begins to rise. The effect on blood pressure is transient, however, and pressure generally returns to the normal range within a few minutes.

Hypertension, bradycardia, and respiratory disturbances have long been noted as concomitants of medullary dysfunction. These disturbances collectively are known as the "Cushing response".(20,21) Respiratory rate disturbances seen with cerebral missile injury usually occurred virtually instantaneously with missile passage. This argues strongly that the wound process exerts a direct, mechanical effect upon brainstem respiratory centers. In contrast, the cats usually became hypertensive and bradycardic from 2 to 20 seconds after wounding. These responses, therefore, are probably mediated by reflex arcs affecting vasomotor and cardiac pacing centers. Other investigators have determined that the post injury hypertensive response may be abolished if the spinal cord is sectioned at C-3.(22)

The exact mechanisms by which a missile wound of the cerebral hemisphere exerts its effect upon the distant brainstem are unknown but several are possible: 1) hydrostatic overpressures consequent to missile passage through the hemisphere may subject the medulla to abnormal movements thereby stimulating/inhibiting medullary centers for blood pressure, pulse, and respirations. 2) the "shock wave" associated with missile passage through brain tissue might also adversely affect medullary function. The cat has a bony tentorium and richocet of the missile off this structure in close proximity to the brainstem may focus shock waves upon the medulla and, so, accentuate the observed changes in respirations, blood pressure and pulse. We will check for this possibility by altering missile trajectory to prevent the steel ball from inpacting upon the tentorium near the brainstem. 3) either intracranial overpressures or shock wave associated with missile passage might lead to medullary ischemia and hypoxic damage to medullary respiratory centers in particular. 4) We have demonstrated that the right hemisphere wound disrupts the blood-brain barrier in the brainstem, a "distant effect" of wounding, (see BLOOD-BRAIN BARRIER STUDIES, Section 10). This would allow substances present in plasma and normally excluded from brain extracellular fluid (ECF) to leak into the medullary ECF compartment. While such leakage would not be expected to cause immediate cessation of respirations, the accumulation of substances from plasma in the brainstem might prevent the later resumption of respirations in susceptible animals.

B. Intracranial Pressure (ICP)

In discussing ICP we may consider immediate and sustained elevations. After wounding all animals showed an immediate rise in ICP, the percentage rise of which was roughly proportional to energy deposit by the missile, table 9 and figure 24.

Table 9: CORRELATION OF IMMEDIATE, POST WOUNDING ICP AND ENERGY DEPOSIT (JOULES) BY A WOUNDING MISSILE: (ICP= X ± SD; 5 cats each group)

Test Groups	ICP (mmHg)	% increase in X ICP
Controls	6.7 ± 2.5	0
0.9J	24.6 ± 13.2	+221
1.4J	36.8 ± 24.0	+495
2.4J	62.6 ± 35.9	+1115

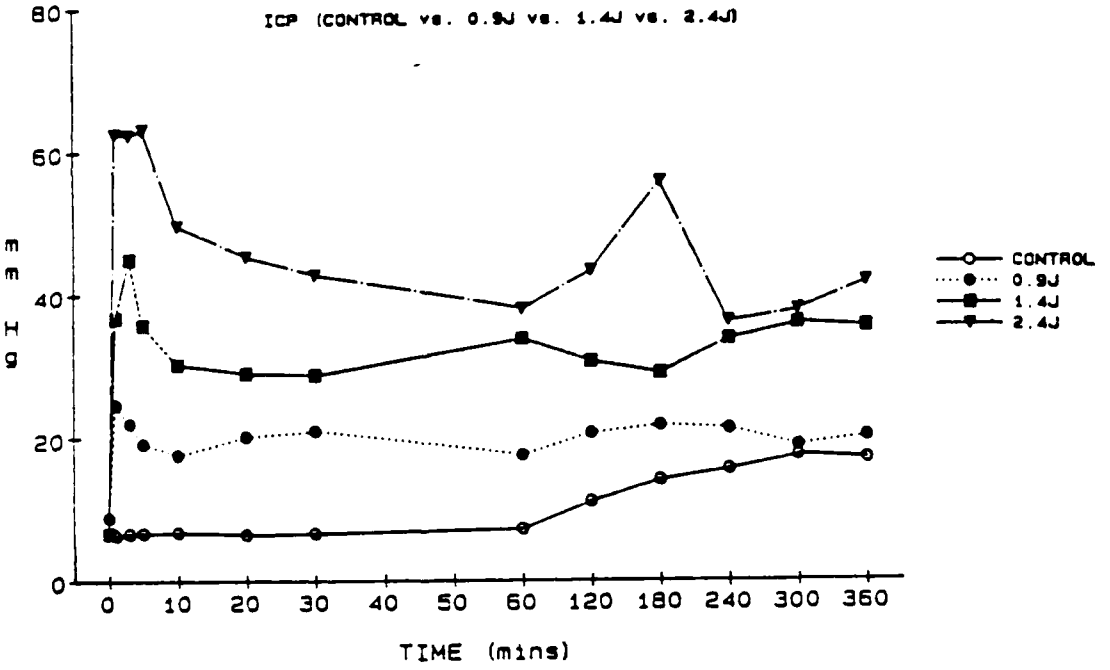


Figure 24: Immediate and sustained intracranial pressure rises caused by missiles of increasing energy.

Not only were the immediate ICP elevations proportional to missile energy deposit but the sustained ICP elevations also generally corresponded to energy deposit as well.

Cats wounded at 0.9 Joules had moderate increases in ICP to about 18 to 22mmHg; those wounded at 1.4 Joules had sustained intracranial pressures of 29-35mmHg while animals wounded at 2.4 Joules had ICPs of about 38-50mmHg. At this point we do not know whether the elevated ICP per se accounts for the high mortality of the 2.4 Joule wounds nor whether steps taken to reduce ICP (e.g. mannitol, hyperventilation) right after wounding might decrease their lethality.

These immediate and sustained ICP elevations after wounding must not be confused with instantaneous intracranial overpressures generated by missile passage through the brain. Intracranial overpressures associated with missile transit develop in approximately 0.1 millisecond and cannot be recorded on our physiograph because of their brief duration. The elevations in ICP which we observed occurred over much longer time periods and were from intracranial physiological-anatomical events associated with brain wounding. These increases could have come from several sources: 1) from associated intracranial hemorrhage; 2) from an increased rate of CSF formation or decreased rate of CSF absorption; 3) from associated vasogenic brain edema or 4) from an increase in the intracranial vascular volume.

Measuring the amount of intracranial bleeding associated with the brain wound is difficult. Our experience, however, indicates that higher energy wounds are not necessarily associated with more intracranial bleeding; sometimes lower energy wounds have larger intracerebral clots than do the higher energy lesions. A lower energy missile would be just as likely to sever a cerebral vessel as would a higher energy one. Thus, if intracranial bleeding alone were responsible for the observed sustained increases in ICP one might expect a more random distribution of ICP elevations among groups instead of a stepwise increase in ICP change with each incremental increase in energy deposit. We, therefore, are inclined to discount associated intracranial hemorrhage as being the major factor accounting for post wounding ICP elevations.

We have no reason to suspect that a hemispheral brain wound would affect either CSF formation or absorption.

We evaluated cats in this series of experiments for the first six hours after wounding. Our very comprehensive experiments on post-wounding vasogenic brain edema indicate that no significant brain edema occurs within 6 hours of wounding for either 0.9J or 1.4J missiles, (see BRAIN WATER AND ELECTROLYTES, Section 11). Increased brain water does not account for this early rise in intracranial pressure.

We, thus, feel that an increased intracerebral vascular volume following wounding may account for the stepwise increase in ICP with increasing wound energy. Cerebral hyperemia has been hypothesized following closed head injury.(23,24,25) This possibility following a missile wound to the brain should be explored because if the intracerebral vascular volume does increase after brain wounding, medical therapies which expand the intracerebral vascular space further may prove detrimental to the brain by elevating the ICP further. In Vietnam many soldiers who received a brain wound also received bodily wounds from which they often exsanguinated.(3) In such patients vigorous treatment of hemorrhagic shock by larger amounts of volume expanders than necessary could conceivably have proved detrimental to function of the wounded brain if brain microcirculation were already expanded from vasoparalysis associated with brain wounding. In the future, knowing the microcirculatory status of the wounded brain may prove very important and may govern the optimal fluid management of soldiers who recieve, simultaneously, severe somatic and brain wounds.

C. Cerebral Perfusion Pressure (CPP)

CPP is defined as Mean Arterial Pressure (MAP) minus Intracranial Pressure (ICP): CPP=MAP-ICP. CPP represents the net hydrostatic pressure which forces blood through the brain. Increases in ICP may reduce CPP and, potentially, cerebral blood flow (CBF). CBF is reduced when CPP falls below the level of CBF autoregulation or when CBF autoregulation is abolished. Under these circumstances CBF is determined by the actual arterial perfusion pressure.(26) Zwetnow has shown that serious and long lasting metabolic derangements occur in the brain when CPP is reduced below 40mmHg.(27)

In our experimental model a progressive reduction in CPP occurred with increasing missile energy, figure 25.

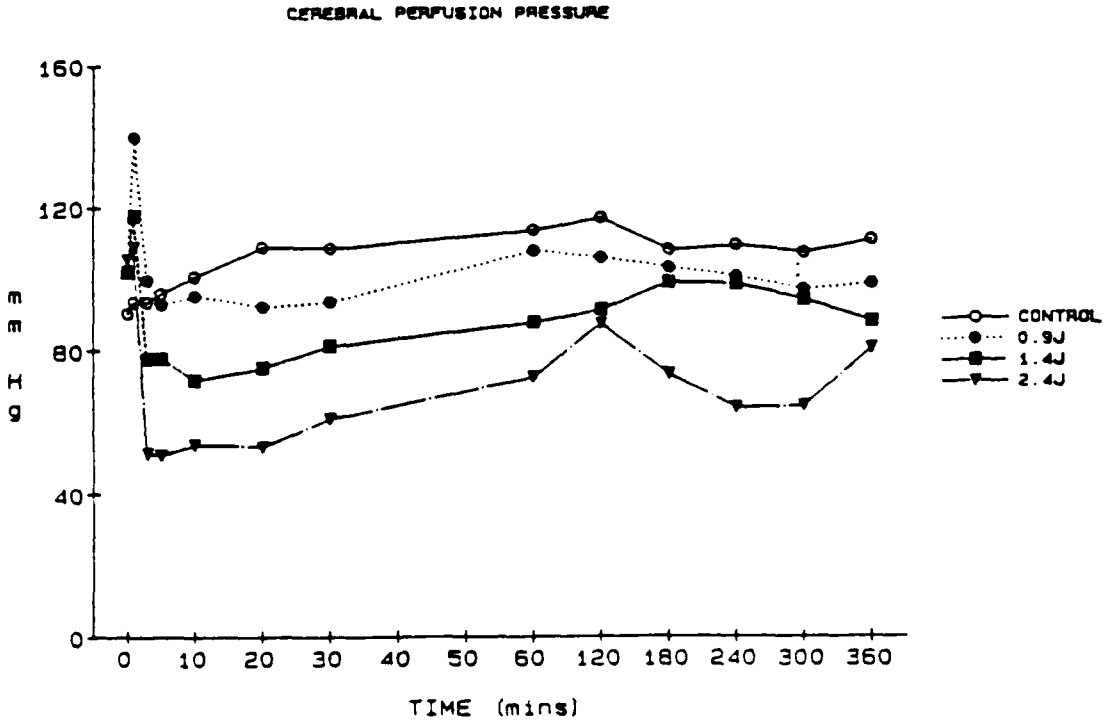


Figure 25: Cerebral Perfusion Pressure falls with brain wounds of increasing energy.

Cats wounded at 2.4 Joules incurred severe CPP reductions into the range where severe metabolic disturbances may have been expected. Perhaps this severe CPP reduction contributed to the high mortality observed in this group. As systemic blood pressure was near normal in all brain-wounded cats after an initial transient rise (figure 23) sustained CPP reductions resulted from prolonged ICP elevations after wounding.

As has been discussed above, discovering the true cause of post-wounding ICP elevations and controlling them may diminish the mortality associated with severe brain wounds.

D. Pulmonary Function

1) Arterial Blood Gases

We have demonstrated that brain wounding may exert a profound influence upon "central" (medullary) respiratory drive mechanisms. Additionally, we have monitored arterial blood gases after wounding in 15 cats and have determined that brain wounding also may be associated with significant "peripheral" (pulmonary) effects as well: hypoxia, hypercarbia, and acidosis. While often these effects accrue from the apnea itself, sometimes they are not the result of decreased central respiratory drive mechanisms, table 10.

Table 10: THE EFFECT OF BRAIN WOUNDING UPON ARTERIAL BLOOD pO_2, pCO_2 AND pH

		Pre Wounding				1 Minute Post Wounding			
Wound Energy	Cat No.	Resp Rate	pO_2	pCO_2	pH	Resp Rate	pO_2	pCO_2	pH
0.9J	219	18	100.0	37.8	7.38	0	121.8	26.4	7.35
0.9J	227	14	81.2	31.8	7.48	8	63.7	35.7	7.41
*0.9J	231	8	82.7	46.8	7.36	10	65.7	50.4	7.28
0.9J	233	12	82.6	42.0	7.32	0	59.8	39.7	7.34
0.9J	239	16	102.9	40.8	7.32	20	121.7	39.9	7.35
1.4J	225	20	101.6	29.9	7.43	0	59.4	41.4	7.37
1.4J	228	24	74.3	40.7	7.33	19	71.7	41.9	7.33
1.4J	234	8	109.8	38.0	7.36	0	39.3	46.9	7.26
1.4J	237	14	113.6	40.9	7.30	0	46.8	50.9	7.25
*1.4J	243	10	111.4	42.3	7.40	14	61.2	51.9	7.30
2.4J	220	12	60.8	32.7	7.40	12	47.1	31.5	7.36
2.4J	223	12	127.5	44.0	7.37	6	120.0	36.6	7.33
2.4J	236	13	91.5	43.5	7.30	8	51.5	48.7	7.27
2.4J	241	12	105.8	44.6	7.32	0	57.9	50.3	7.36
*2.4J	244	16	120.6	40.1	7.38	21	72.9	50.9	7.31

*animals exhibiting significant decreased arterial pO_2, hypercarbia, and decreased pH without "central" respiratory depression.

Three cats(*) exhibited increased respiratory rate after wounding and simultaneously had decreased arterial pO_2s and pHs plus increased pCO_2s indicating lack of oxygen and carbon dioxide exchange during this interval. This clearly indicates a direct effect of brain wounding upon lung function, i.e. a "peripheral" action. Cats with a "central" respiratory depression may also have had simultaneous "peripheral" lung dysfunction as well so the percentage of cats having peripheral lung decompensation after a brain wound may, in reality, be greater than the 20% we have demonstrated here (3/15).

Brain injury may result in neurogenic pulmonary edema and pulmonary decompensation by several possible mechanisms.(28) These changes may occur acutely or in a delayed fashion. Severe CNS insults (including, as we have demonstrated, experimental missile wounding, figure 23) may be associated with sharp rises in systemic arterial pressure and a correspondingly high peripheral resistance which may overload the left ventricle of the heart. This may lead to increased pulmonary vein pressure, elevation of pulmonary microvascular pressure and lung edema. Experiments also have shown that brain injury may directly cause pulmonary venous constriction and pulmonary microvascular hypertension. Increased ICP per se as well as increased vagus nerve output with brain injury may also adversely affect left ventricular function and increase pulmonary venous vein pressure. Besides these hemodynamic effects, brain injury also may cause an increase in lung vascular permeability. Investigators have hypothesized that the combination of increased lung capillary permeability plus pulmonary vascular changes may lead to decreased lung function or frank neuogenic pulmonary edema following brain injury. While pulmonary vascular changes may be mediated by direct neural stimulation of the pulmonary vasculature, vasoactive substances (e.g. catecholamines or prostaglandins) released following brain injury may also lead to pulmonary vasoconstriction or increases in lung permeability.(28) We have demonstrated large elevations in plasma thromboxane one hour after missile injury, see BRAIN AND CSF PROSTAGLANDINS, Section 12. Brain stem areas (A5, upper medulla; A1, ventrolateral medulla; nucleus of the solitary tract; area postrema) plus the hypothalamus and the cervical spinal cord have been shown to participate in the initiation of neurogenic pulmonary edema.(28) This report presents ample evidence that missile wounds of sufficient energy profoundly affect the brainstem. Thus, transfer of energy from the missile to critical brainstem areas may also contribute to the occurrence of neurogenic pulmonary edema.

Our experiments indicate that a missile wound to the brain may profoundly affect the brain-lung axis. In addition to frequent apnea,(tables 1 and 2) among 91 brain-wounded cats, we have observed at least 3 mild cases of pulmonary decompensation plus 2 fulminating, fatal instances of neurogenic pulmonary edema. These findings suggest that about 5% of brain wounds will be associated with varying degrees of pulmonary failure which may lead to the death of the brain-wounded individual. Ascertaining the mechanisms of this pulmonary failure and instigation of appropriate treatment may lower the mortality from brain wounds.

To our knowledge the above data are the first demonstration of this pulmonary effect with an experimental missile wound.

E. Systemic Effects

Although brain wounding undoubtedly incites a multiplicity of systemic responses we were readily able to evaluate only changes in blood glucose* and hematocrit.

1) Arterial Blood Glucose

Blood glucose rose after wounding, table 11. (See also Appendix: tables 55-58 and figures 79-82) Rather large standard deviations occurred in blood glucose measurements because the cats varied considerably in their normal prewounding blood glucose levels. As soldiers may have eaten prior to battle, for realism, no amimals were fasted before the experiments. Control cats, which were not wounded, showed a 19% to 65% rise in arterial blood glucose during the first experimental hour in the stereotaxic frame owing, no doubt, to wearing off of anesthesia, stress, and gluconeogenesis. All told, 14 of 15 wounded cats demonstrated a post wounding rise in blood glucose. These increases were variable and occurred at different times during the first hour after wounding. Seven of 15 wounded cats showed post-wounding blood glucose elevations greater than 65% (range: 75% to 129%). Table 11 shows the maximal rise in arterial blood glucose and the time frame from wounding until maximum elevation. These data indicate no correlation between wound energy and the percent rise in arterial blood glucose, but the time to peak elevation may be reduced with increasing missile energy.

Table 11: RISE IN ARTERIAL BLOOD GLUCOSE AFTER WOUNDING
(X ± SD; 5 cats each group)

Test Groups	Control Blood Glucose ($mg\ dl^{-1}$)	Maximum Blood Glucose ($mg\ dl^{-1}$)	Time to Maximum Elevation (min)	Blood Glucose Elevation (% Change)
Controls	89.4 (±18.8)	111.8 (±26.7)	60	+25.1 (±19.9)
0.9J	87.6 (±31.0)	148.0 (±71.7)	60	+63.8 (±35.8)
1.4J	90.2 (±16.0)	114.4 (±28.4)	30	+25.9 (±13.1)
2.4J	85.6 (±21.4)	141.4 (±60.6)	20	+61.7 (±34.2)

Stress and intracranial lesions are commonly associated with a rise in arterial blood glucose and our model of brain wounding is no exception.(29,30) Theoretically, these large elevations in blood glucose could prove detrimental to brain function if an element of ischemia were superimposed upon the brain wound. Several authors have shown that elevated blood glucose increases ischemic brain damage presumably from increased lactic acid production in the damaged brain, concomitant acidosis, and local tissue damage.(31,32)

* Blood glucose determinations were made by Ames Dextrometer #5570 Ames Division, Miles Laboratories, Inc., P.O. Box 70, Elkhart, Ind., 46515

2) Hematocrit

The hematocrit (HCT) rises which we documented after wounding were transient and almost all occurred within the first post-wounding minute. These hematocrit rises were abolished by splenectomy and, thus, the source of the increased circulating RBCs following brain wounding was the spleen. Table 12 summarizes these early, transitory hematocrit elevations: again, no correlation exists between wound energy and the percent change in post wounding hematocrit. Full data on these hematocrit changes are presented in Appendix tables 59-62 and figures 83-86.

Table 12: HEMATOCRIT CHANGES AFTER WOUNDING
(X ± SD)

Test Groups	Control HCT	Maximum Post-Wounding HCT	Time to Maximum Post-Wounding HCT Peak (Min)	% Change
control(5)	26.4 (±1.5)	-	-	+6.9 (±7.3)
0.9J(4)	31.6 (±4.9)	38.9 (±6.9)	1	+24.0 (±21.9)
1.4J(5)	32.3 (±3.6)	40.8 (±5.0)	1	+27.7 (±22.6)
2.4J(5)	32.8 (±2.9)	40.5 (±4.9)	1	+23.4 (±8.4)
2.4J(3) (Splenectomy)	27.7 (±4.3)	27.9 (±3.1)	3-10	+0.47 (±0.5)

( ) Number of cats

Other investigators have shown that the arterial resistance and venous capacitance vessels in the capsule of the spleen have a dense sympathetic adrenergic innervation that, when excited, results in contraction of the vascular capsular and trabecular smooth muscle which expels blood from the spleen. In the cat stimulation of splenic nerves results in the discharge of large volumes of splenic blood having a hematocrit of 70% to 80%.(33) In our model the brain wound presumably causes a sympathetic disharge to the spleen. This effect must be rather direct because usually the hematocrit rises occurred within one minute of wounding. To our knowledge, this is the first demonstration of increased arterial hematocrit following brain wounding.

We know of no information on the subject for man. If such hematocrit elevations were to occur in man they might be detrimental because increased hematocrit would slow capillary blood flow in regions about the wound. This could lead to ischemic brain damage in addition to mechanical damage associated with wounding.(34) Evidence suggests, however, that the normal human spleen does not have a significant role as a blood reservoir so corresponding increases in arterial hematocrit for humans following a brain wound may not occur.(33)

10. BLOOD BRAIN BARRIER STUDIES:

The blood-brain barrier (BBB) is constituted by endothelial cells of brain capillaries and provides one of the chief homeostatic mechanisms of the brain. The BBB regulates the passage of various molecules from inside brain capillaries to the brain extracellular space and from the brain extracellular space into brain capillaries.(35)

Because of its ready visibility, Evans blue dye has been widely used to qualitatively evaluate BBB integrity.(36,37,38) When injected intravascularly Evans blue attaches to plasma albumin molecules and, hence, essentially has a molecular weight of 68,000 Daltons. If the BBB is intact, intravascular Evans blue dye molecules will not pass from the inside of a brain capillary to the outside and into the brain extracellular space. Normally, therefore, if an animal is injected intravenously with Evans blue dye the brain parenchyma shows no blue staining. If the BBB is damaged, however, intravascular Evans blue dye will leak from the capillary compartment into the substance of the brain and stain the brain parenchyma blue. Missile injury damages brain parenchyma and disrupts the integrity of the BBB.

Method: We evaluated BBB integrity after wounding by giving several milliliters of a 2% solution of Evans blue dye(*) intravenously to the cats at the time of wounding or at various times thereafter. From minutes to days after wounding and Evans blue dye administration (depending upon the question we were attempting to answer), we painlessly euthanized the animals, perfused-fixed, and removed their brains. Following further fixation we sliced and photographed the brains to evaluate BBB breakdown after missile wounding.

We asked 3 main questions in this study: 1) Does the BBB breakdown only about the missile track or does breakdown occur as well at a distance from the actual wound? 2) Is the extent of BBB breakdown about the missile track related to the deposit of missile energy? 3) When does the damaged BBB regain its integrity to Evans blue dye?

1. Distant Effects

Evaluation of many brain wounds in our experimental animals indicates that BBB breakdown following wounding occurs not only about the wound track, as would be expected, figure 26, but also in the brainstem, particularly in the ipsilateral colliculus, figure 27.

* Sigma Chemical Company, St. Louis, MO, 63178

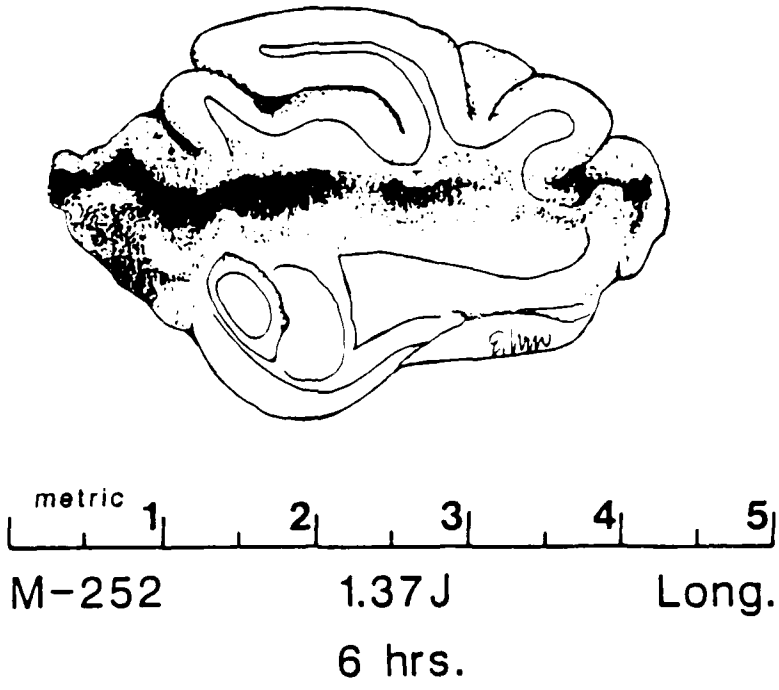


Figure 26: The cerebral hemisphere has been sectioned along the missile track and extravasation of Evans blue dye from the track is evident. Frontal pole is to the right. Stippling represents Evans blue dye extravasation. Line drawing of brain photograph.

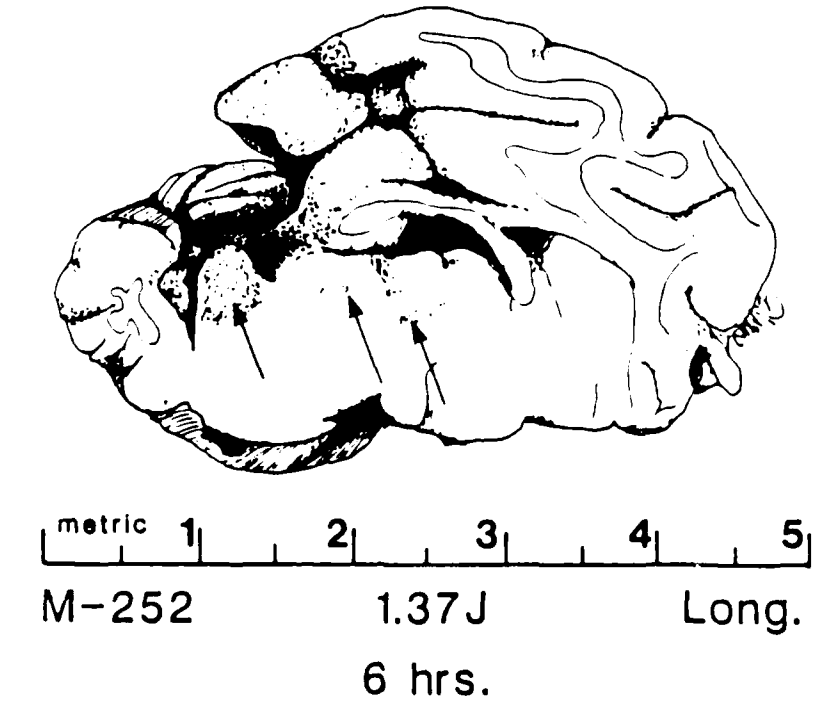


Figure 27: Longitudinal section of brainstem showing extravasation of Evans blue dye in the brainstem and right superior colliculus (arrows). Frontal pole is to the right. Stippling represents Evans blue dye extravasation. Line drawing of brain photograph.

In the preceding section we have shown that brainstem dysfunction (Cushing response) is almost universal following penetrating missile injury. These Evans blue dye studies indicate that not only does a physiological change occur in the brainstem but that a frank, anatomical disruption of the BBB within the brainstem may take place after brain wound. BBB breakdown within the brainstem thus exposes brainstem neurons to substances from the plasma with which they ordinarily would not come into contact. Conceivably, plasma molecules could injure brainstem neurons or prevent them from recovering from what ordinarily would have been a minor, transient injury caused by the mechanical effects of the missile impact.

2. Wound Energy and BBB Breakdown

We can find no correlation between the energy of wounding and the extent of BBB disruption around the wound track as determined by Evans blue dye studies, figure 28. Indeed, in some instances an inverse relation seemed to exist: the greater the missile energy, the less the Evans blue dye leakage along the missile track. While this seems paradoxical, at least two ready explanations exist: 1) Possibly the higher velocity (energy) missiles slow down less in the brain until they impact against the inner table of the skull. Less slowing would mean less energy deposit along the missile track, hence, less brain disruption, and less BBB breakdown. 2) Possibly the higher energy wounds are associated with vasospasm and diminished circulation about the wound track. If this were true, intravascular Evans blue dye simply could not reach the wound track to leak out into the brain parenchyma.

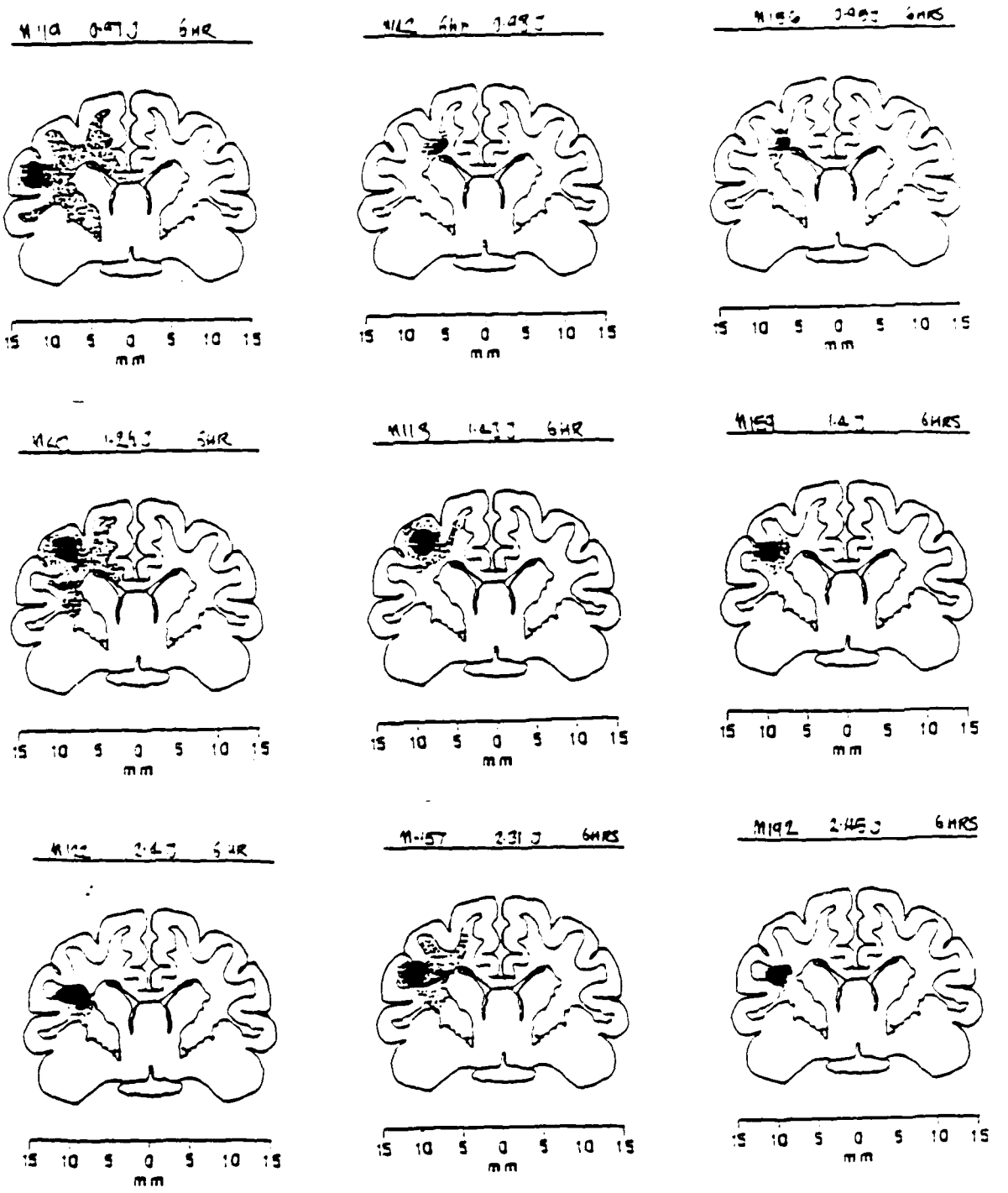


Figure 28: Extravasation of Evans blue dye from damaged brain caused by missiles of increasing energy. No correlation apparently exists between missile energy of deposit and the amount of Evans blue dye leakage. (Line drawings of brain slice V-4 from 9 brain-wounded cats)

3. Repair of the Damaged BBB

Eleven cats were wounded at 0.9 Joules and then perfused intravenously with Evans blue dye for 6 hours either immediately following injury or 24,48, or 72 hours after wounding. These experiments revealed that a small amount of Evans Blue dye leaked into the brain up to 24 hours after wounding but that by 48 hours no dye leakage occurred, figure 28, 29.

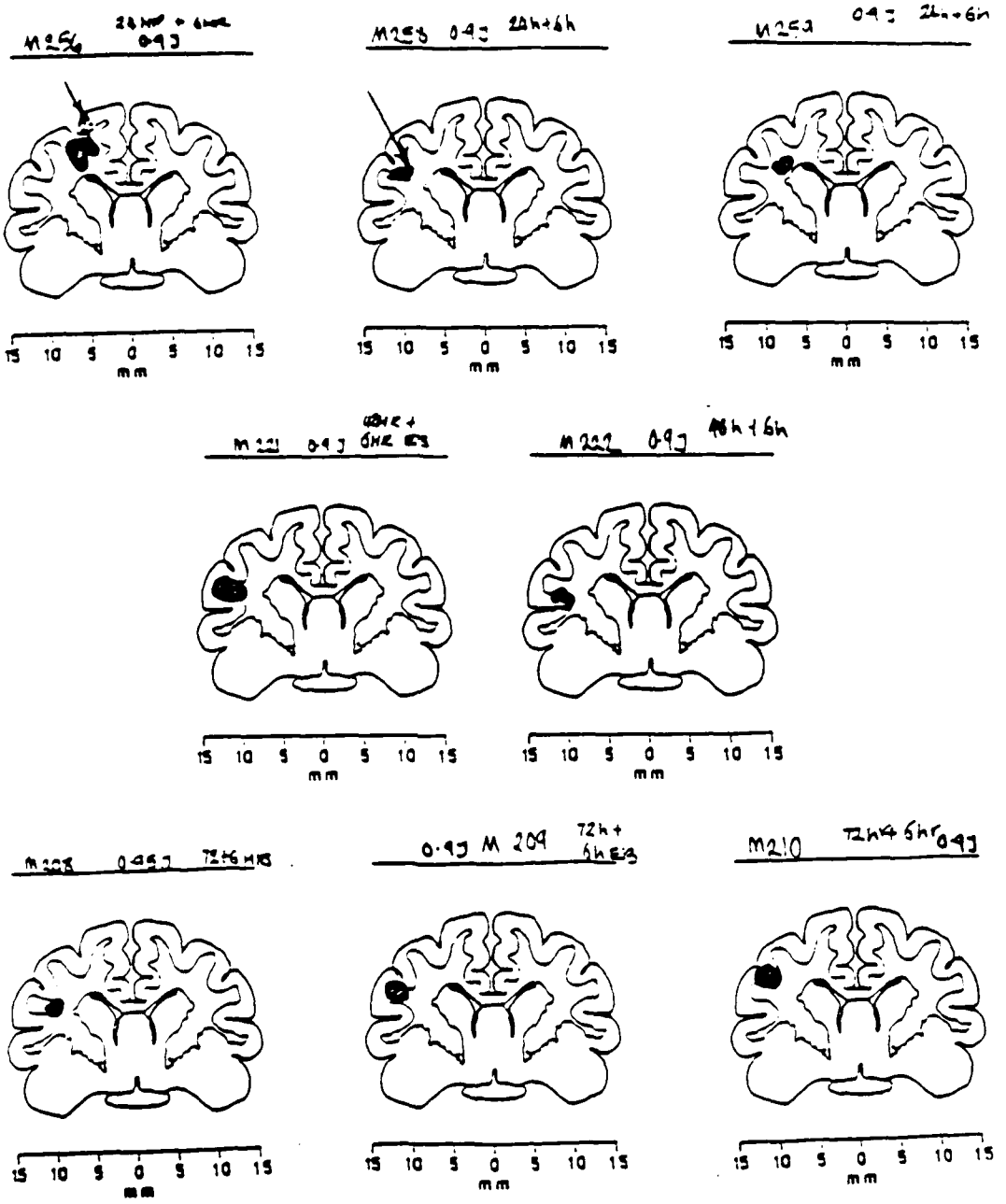


Figure 29: Repair of BBB after wounding. These cats were wounded at 0.9 Joules. Evans blue dye leakage from damaged BBB is evident six hours after wounding. Only a trace of dye leakage is evident at 24 hours (note arrows in two of the three sections) while none was apparent at 48 hours. The damaged BBB was largely reconstituted preventing egress of large molecules later than 24 hours after injury. (Line drawings from photographs of brain slice V-4).

The implication of these studies is that the BBB had repaired itself at 24-48 hrs at least to large sized molecules. In this respect BBB reconstitution after missile injury is quite like that found after the commonly employed cold lesion.(39)

Knowledge of BBB repair times following brain wounding is important because BBB breakdown causes vasogenic brain edema and significant vasogenic brain edema may impair brain function. Vasogenic brain edema associated with missile injury will persist until the BBB can reconstitute its integrity: plasma and plasma constituents including water will leak out into the brain until capillary endothelial repair is complete. On the basis of these blood-brain barrier studies, we conclude that vasogenic brain edema associated with a 0.9J missile wound should begin to recede after 24-48 hours. (See BRAIN WATER AND ELECTROLYTES, Section 11). We are currently evaluating whether a 1.4J wound will cause loss of BBB integrity for a longer period of time.

Evaluation of the BBB by Evans blue dye allows one to document only rather large BBB defects because this method visualizes the escape of plasma albumin (MW 68,000 D) into the brain. With BBB disruption not only will large molecules leak into the brain but small, potentially potent ones will as well, (eg dopamine or other neurotransmitters). In the future, by means of autoradiography and ^{14}C sucrose (MW 342 D) we will evaluate whether the loss of BBB integrity to small molecules is more widespread than that for large ones which we have observed by Evans blue dye. If so, this would have important ramifications: widespread leakage of small molecular weight, biologically active substances into the brain from plasma could alter brain function directly by impairing neurons or indirectly by causing vasospasm and neuronal ischemia.(40,41)

11. BRAIN WATER AND ELECTROLYTES

Brain edema has been extensively studied after a cold lesion to the brain and experiments have determined that this injury disrupts the blood-brain barrier (BBB) which causes plasma constituents including sodium, albumin, and water to leak into the brain extracellular space.(39,42,43,44,45) Brain edema from BBB breakdown is called "vasogenic" edema and is characterized by increased tissue water and sodium with no increase in potassium.(46) Brain edema has been reported after brain wounds but its characteristics, magnitude, site of occurrence, resolution and correlation with clinical status have heretofore been totally unknown.(47,48) Because brain edema following missile injury could be potentially dangerous and lead to increased neurological deficit or even death from increased intracranial pressure, the principal investigator reasoned that delineation of brain edema caused by a missile wound to the brain would be of fundamental importance. Thus, we have determined the development and resolution of brain edema associated with missile injury from 6 hours to 7 days following wounding. This study, encompassing 72 cats, forms a main focal point of contract DAMD 83-C-3145

Method: After wounding, (see section 3 for details of wounding) the animals were painlessly sacrificed at various times (6 hours to 7 days) and their brains quickly removed under a humidity hood which had been determined to allow only 0.5% water loss from cat brain samples in 20 minutes. Thirteen brain areas were sampled in each cat within about 10 minutes and these brain specimens were placed into tared, borosilicate weighing vials which were then capped. After reweighing, the vials were uncapped and placed into a drying oven for 48 hours. All brain specimens were then dried to a constant weight. After drying, the vials were put into a dessicator, allowed to cool, and again reweighed. Water content of the brain specimens was calculated:

$$\% \text{ water} = \frac{\text{Wet Weight} - \text{Dry Weight} \times 100}{\text{Wet Weight}}$$

Next, the brain char was ground with a glass rod and an aliquot of 0.75N HNO_3 added to leach out the contained electrolytes. The specimens were agitated for 48 hours and the 0.75N HNO_3 supernatant decanted and aspirated through a flame photometer(*) for sodium and potassium determinations. Electrolyte concentrations in this report are expressed as milliequivalents per milligram of dry weight.

We evaluated brain water, sodium, and potassium in the following groups of cats:

1. Controls (4 cats): sacrificed immediately after anesthesia and surgery. (Total anesthesia time less than 45 minutes).

2. Additional control cats (20 cats: 4 cats each group) sacrificed at the following times after anesthesia and surgery: 6 hrs, 24 hrs, 48 hrs, 72 hrs, 168 hrs (1 week)

3. Cats wounded at 0.9 Joules and sacrificed at the following times after anesthesia, surgery, and wounding: 6 hrs, 24 hrs, 48 hrs, 72 hrs 168 hrs (1 week). (4 cats each time point)

4. Cats wounded at 1.4 Joules and sacrificed at the following times after anesthesia, surgery, and wounding: 6 hrs, 24 hrs, 48 hrs, 72 hrs 168 hrs (1 week). (4 cats each time point)

5. Rod-injured cats sacrificed at 48 and 168 hours after anesthesia, surgery, and right hemisphere rod injury. (4 cats each time point).

All data were analyzed by analysis of variance. Specific comparisons were made using
Bonferroni statistics.

Results: All brain water and electrolyte data are presented in Appendix tables 63-75. The pertinent point, however, is that significant brain edema consistently occurred only in the white matter of the wounded cerebral hemisphere about the missile track, table 13. (Perusal of the appendix tables reveals intermittent, random significant increases in brain water or electrolytes in occasional other sampled brain areas but these form no discernable pattern and undoubtedly occurred owing to these small N in each sample group).

* IL443, Instrumentation Laboratory, Lexington, Mass 02173

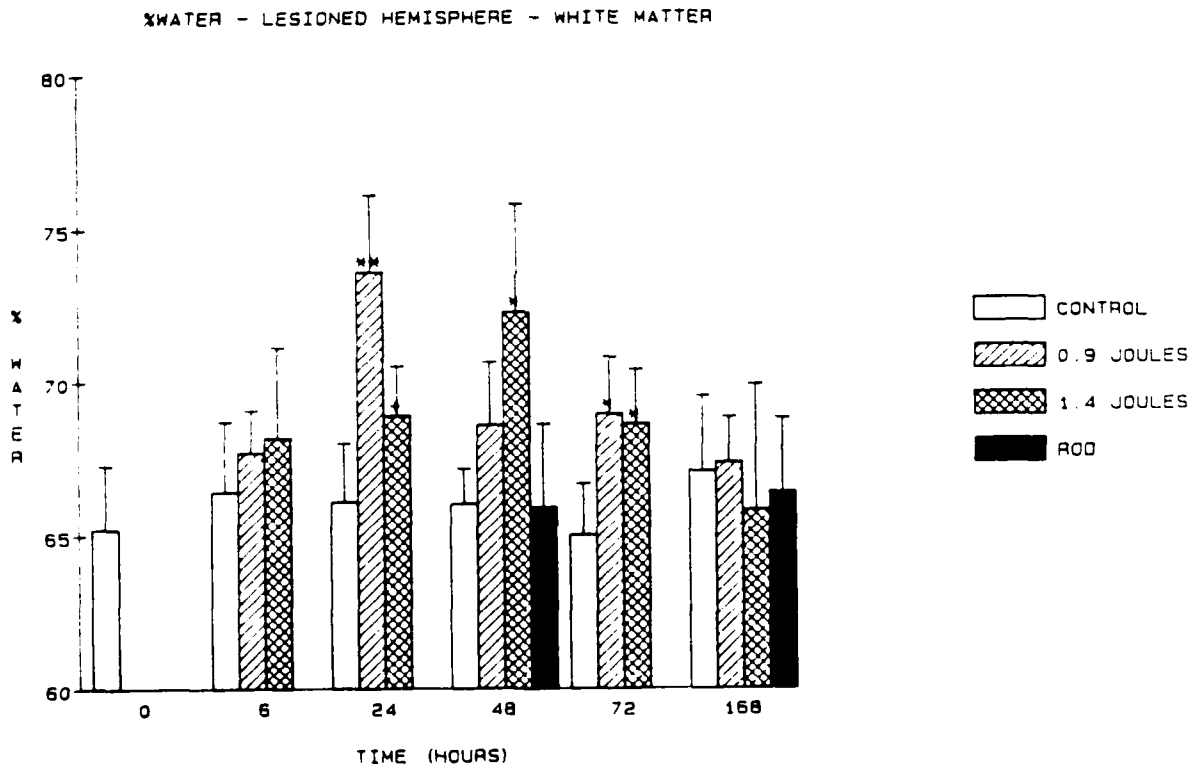
		%WATER	Na^+ (mEq/Kg dry weight)	K^+
0 HOUR				
CONTROL	mean	65.22	147.36	253.14
(4)	S.D.	2.09	6.03	13.86
6 HOUR				
CONTROL	mean	66.43	157.25	264.12
(4)	S.D.	2.30	12.27	22.55
0.9J	mean	67.71	186.78	251.65
(4)	S.D.	1.37	37.71	19.93
1.4J	mean	68.19	173.76	256.30
(4)	S.D.	2.95	13.74	27.89
24 HOUR				
CONTROL	mean	66.10	155.20	261.15
(4)	S.D.	1.90	7.87	16.60
0.9J	mean	73.61**	252.79**	280.26
(4)	S.D.	2.48	32.07	56.75
1.4J	mean	68.91	215.15*	218.75
(4)	S.D.	1.61	44.23	33.43
48 HOUR				
CONTROL	mean	66.05	146.05	234.47
(4)	S.D.	1.14	24.70	29.84
0.9J	mean	68.60+	234.71**	221.79
(4)	S.D.	2.05	40.26	19.54
1.4J	mean	72.26*	254.07*	254.12
(4)	S.D.	3.51	57.27	35.65
ROD	mean	65.93	161.10	260.80
(4)	S.D.	2.70	23.60	23.13
72 HOUR				
CONTROL	mean	65.03	160.42	253.33
(4)	S.D.	1.67	23.26	23.41
0.9J	mean	68.96*	210.43*	233.39
(3)	S.D.	1.86	15.67	25.41
1.4J	mean	68.53*	216.71*	224.94
(4)	S.D.	1.56	29.94	24.71
168 HOUR				
CONTROL	mean	67.11	156.43	276.72
(5)	S.D.	2.45	5.28	16.65
0.9J	mean	67.37	188.59*	253.18
(5)	S.D.	1.48	15.59	11.23
1.4J	mean	65.82	203.20*	213.11*
(5)	S.D.	4.10	36.72	14.37
ROD	mean	66.39	162.38	272.07
(4)	S.D.	2.43	12.25	20.16

** $P<0.01$, * $P<0.05$ as compared to corresponding time control values.
+ $P<0.05$ comparing 0.9J and 1.4J values.

Table 13: Brain water sodium, and potassium in the right cerebral hemisphere white matter of control and wounded cats.

While we observed some increase in brain water in the white matter of the wounded hemisphere 6 hours after wounding, brain edema did not become significant ($p<0.01$) in the white matter of the damaged cerebral hemisphere until 24 hours after the missile wound. Both missile energies caused brain edema but the amount of edema associated with the 1.4J wound was not greater than that seen with the 0.9J missile injury. This excess brain water remained at 48 hours but then began to recede so that one week after injury no significant brain edema was evident.

We evaluated a right cerebral hemisphere rod injury to see whether the amount of brain edema associated with a low energy 2mm diameter rod wound would be different from that caused by a high energy (relatively) 2mm diameter missile wound. The 2mm rod injury produced no measurable brain edema at all. The time course and magnitude of water gain by the white matter of the wounded cerebral hemispehre are shown in figure 30.



Means +/- S.D. ** P<0.01; * P<0.05 of control. + P<0.05. 0.9J v 1.4J.

Figure 30: Brain edema in the wounded hemisphere. The white matter of the missile-wounded hemisphere appears to begin gaining water immediately after wounding. The water gain became significant 24 hours later. Brain edema began receding after 48 hours and had largely resolved by 168 hours (1 week).

Brain sodium also increased significantly ($p<0.01$) in the white matter of the wounded hemisphere 24 to 48 hours after wounding but brain potassium remained unchanged, figures 31, 32.

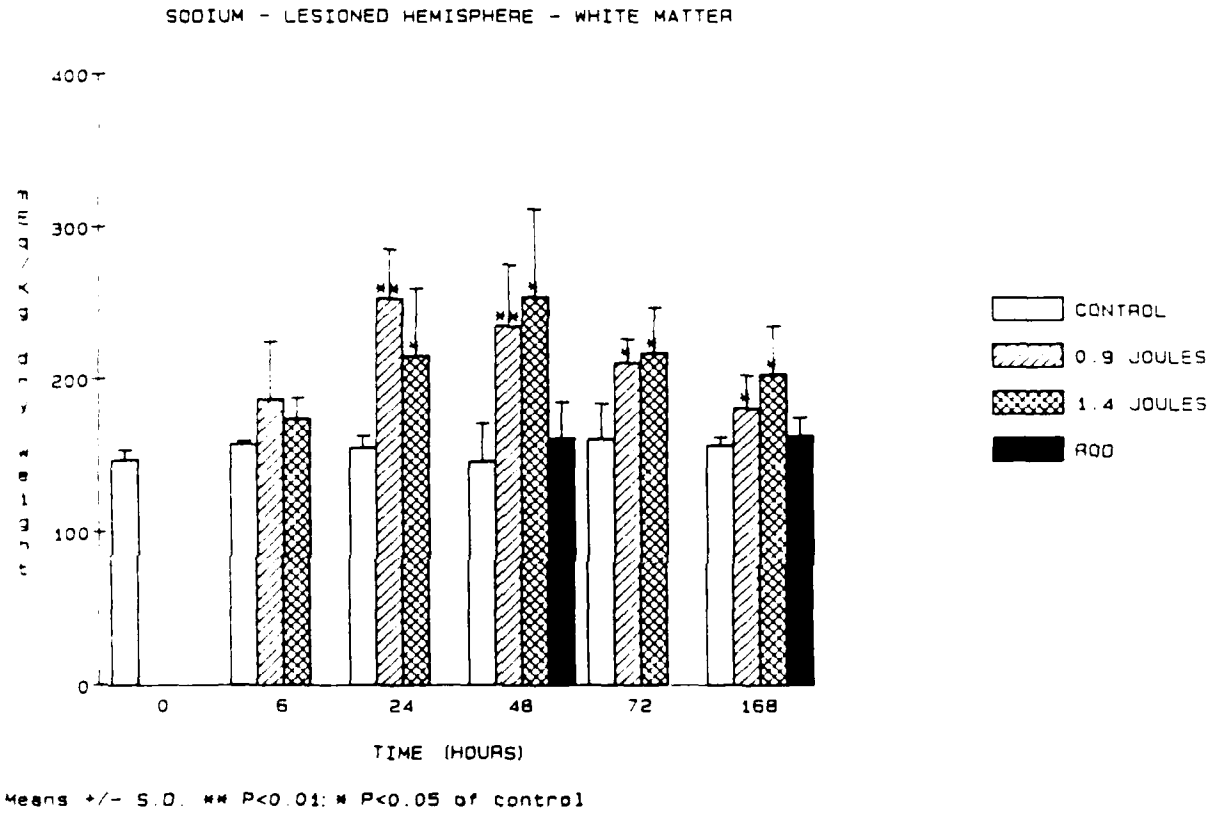


Figure 31: Sodium increased in the white matter of the right (wounded) cerebral hemisphere and became significant 24 hours after wounding.

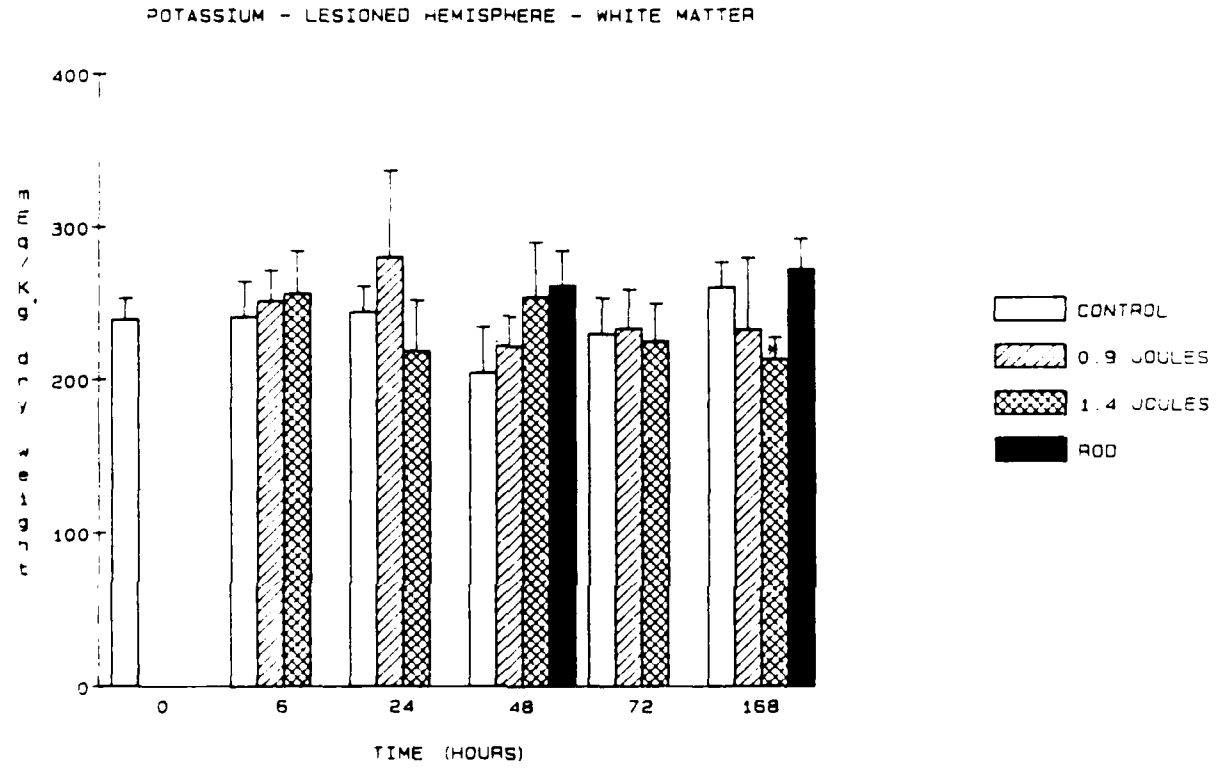


Figure 32: Potassium remained constant and unchanged in the white matter of the right (wounded) cerebral hemisphere. The "significant" decrease at 168 hours is isolated, inexplicable and probably results from the small N in each study group.

These data are consistent with an accumulation of plasma sodium and water in the brain's extracellular space and indicate that missile wounding is associated with "vasogenic" cerebral edema. These brain water and electrolyte results correlate nicely with our Evans blue dye studies which demonstrated a disruption of the BBB lasting 24 to 48 hours. Brain edema does indeed begin to resolve at the time when the BBB reconstitutes itself and is no longer permeable to the Evans blue dye.

Discussion: Brain edema occurred after both the 0.9J and the 1.4J missile wound but the higher energy wound was not associated with more edema than the lower energy one, figure 29. Interestingly enough, edema associated with the 0.9J missile seemed to occur earlier than that with the 1.4J missile. Whether this is a real effect or reflects the small number of animals in each experimental group is unknown. With both wound energies, however, brain edema was maximal from 24 to 48 hours and resolved in 7 days without any treatment whatsoever. This time course to maximal edema formation is quite typical of vasogenic brain edema associated with a cold probe lesion.(39) Our experimental data shows an excellent correlation between the percent change in brain water and rise in brain sodium, figures 33 and 34.

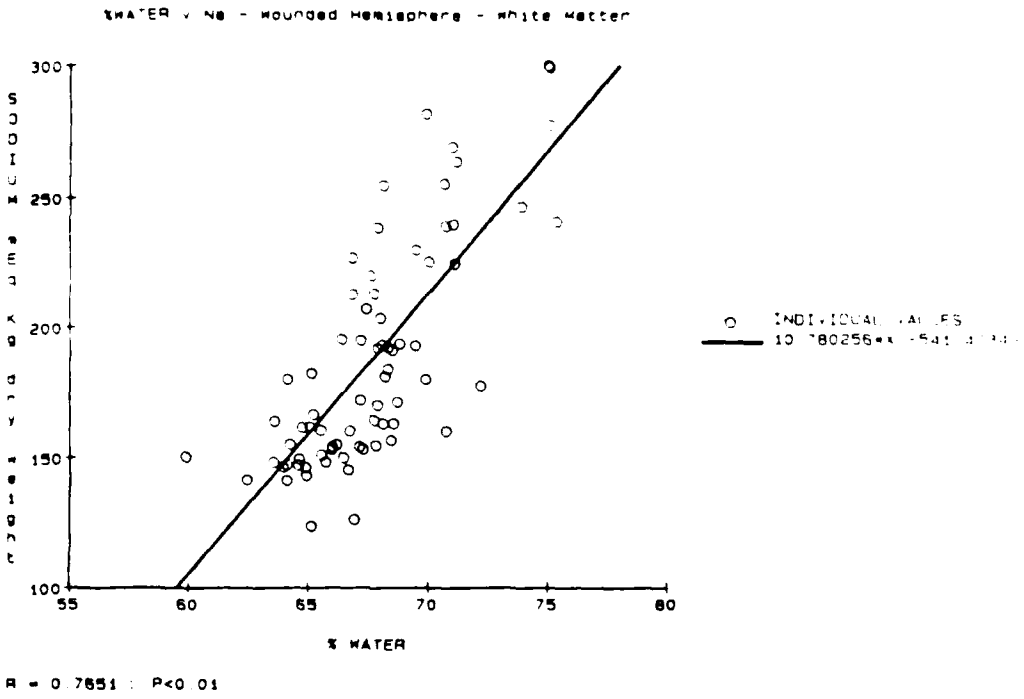


Figure 33: The increase in brain water in the white matter of the wounded hemisphere correlates well with the increase in sodium.

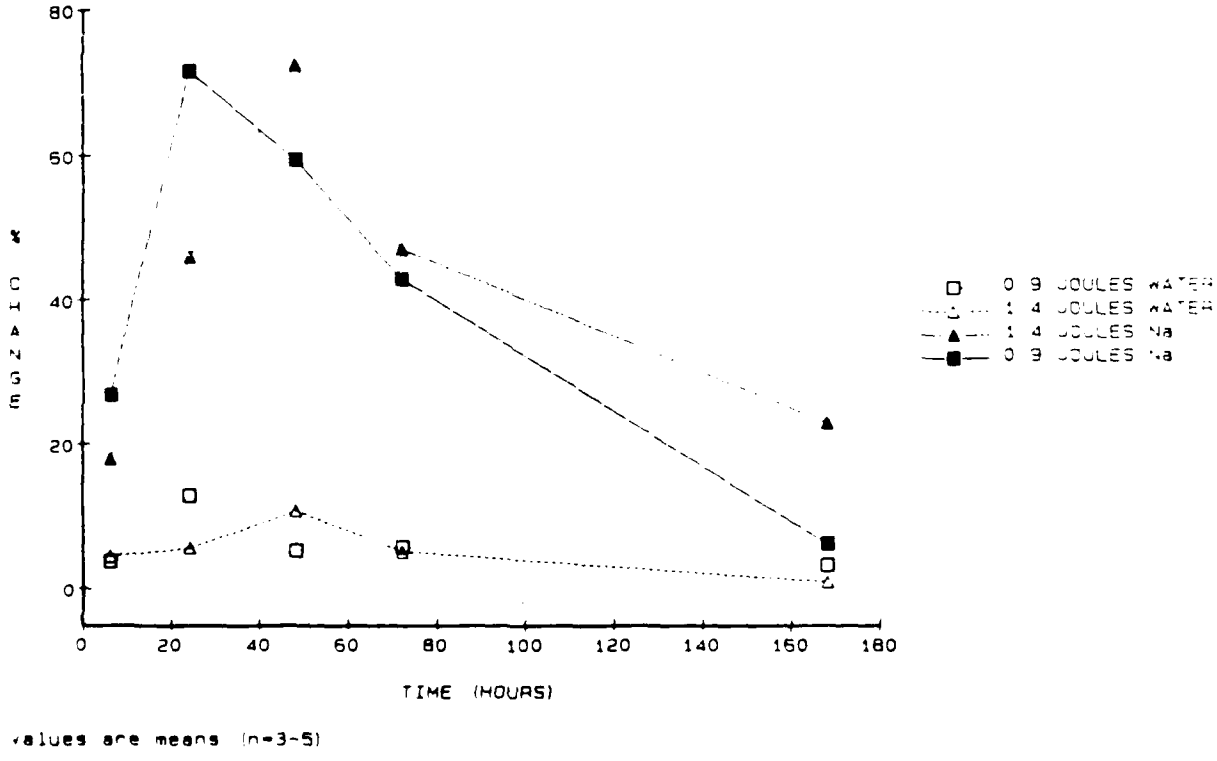


Figure 34: The time courses of sodium and water gain in the white matter of the wounded cerebral hemisphere are congruent.

Albumin from the plasma space also leaks into the brain extracellular space with vasogenic edema. (49,50) We did not try to correlate brain water gain with passage of plasma albumin into the brain. This could have been done with (125)I-albumin injected intravascularly before wounding but the problems of albumin degradation and loss of ^{125}I from the albumin molecule would have made data interpretation difficult.(39)

At present we feel there is no clear relation between the neurological deficits and the development of brain edema. For instance, in a series of other experiments contralateral hemiparesis and circling movements were seen immediately upon awakening following missile wounding in isoflurane-anesthetized cats while the present studies demonstrate that brain edema only becomes significant after 6 hours following the wound.

Our experiments have demonstrated a fundamental difference between the wound caused by a 2mm rod and a 2mm missile. The rod produces a low energy, cutting lesion associated with very little BBB breakdown, no significant brain edema and no distant effects. Missile injury on the other hand deposits all energy in about 0.1m sec. This causes considerable BBB breakdown, significant cerebral edema, and profound brainstem effects.

Extrapolating to the human situation it is evident that a fragment wound to brain is not usually associated with a severe amount of brain edema which proves life threatening. This explains the success of surgery upon the missile-wounded brain especially in days prior to effective anti-edema measures. Once the wound track is debrided there is not a residuum of a large amount of brain edema which could cause fatal hemisphere shifts, brainstem herniations and death. Furthermore, the amount of brain edema associated with missile wounding is self limited because we have demonstrated that the BBB repairs itself and closes in 24 to 48 hours after missile injury. After BBB closure the edema begins to resolve. Clinically, the occurrence of severe edema following a missile wound should make one suspect that the brain has had added insults as, perhaps, hypoxia, hypercarbia, ischemia or infection all of which could potentially increase the amount of brain edema.(46) Concomitant infection, in particular, could greatly increase or delay any resolution of brain edema associated with the missile wound.

Because our data indicated that the usual amount of brain edema associated with missile wound is not severe and spontaneously resolves, we have deferred investigating drug treatments for cerebral edema caused by missiles which we originally proposed to do in contract DAMD-83-C-3145. We felt that more germane investigations could be conducted with allotted time and money. (See BRAIN AND CSF PROSTAGLANDINS Section 12).

12. BRAIN AND CSF PROSTAGLANDINS

Background:

1) Prostaglandins: The biology of the prostaglandins is extremely complex and literature on the subject immense.(51,52,53) Prostaglandins (PG)s form a large class of naturally occurring compounds which are readily released from various tissues, including the brain when they are damaged.(54) PG have a multiplicity of actions on tissues and organs and these effects may be exerted by extremely low concentrations of prostaglandins (10^{-11}M). The biologic activity of PGs is strictly controlled by the specific structure of each PGs. Many prostaglandins seem to act by increasing adenylate cyclase activity which increases intracellular cyclic adenine monophosphate.

2) Arachidonic Acid: Normally, polyunsaturated fatty acids in cell membranes form a small amount of arachidonic acid which is rapidly esterified with acetyl CoA and transferred back to the cell membrane by acyl transferase. The concentration of unesterified arachidonic acid and prostaglandins in the brain under physiological circumstances is very small. In pathologic conditions, including trauma, however, a great increase in free arachidonic acid occurs. The excess arachidonic acid cannot be transformed back into membrane glycerophospholipids and is, instead, metabolized into biologically very potent substances: prostaglandins, thromboxane and leukotrienes. This sequence is indicated in figure 35.

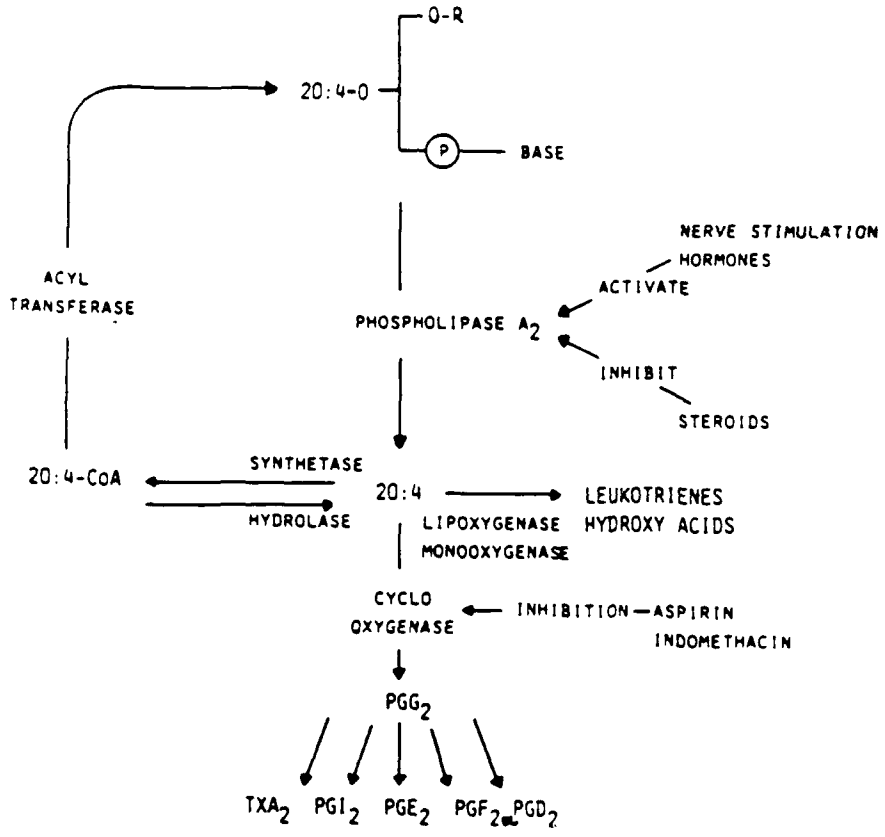


Figure 35: Schematic of arachidonic acid metabolism. Arachidonic acid is released from cell membrane glycerophospholipids for subsequent conversion to oxygenated products or for reesterification into glycerophospholipids in the 2-acyl position.(51)

Some aspects and functions of various prostaglandins, and thromboxane are listed in table 14.(51,52,53)

Table 14: SOME COMMON CYCLOOXYGENASE PRODUCTS AND THEIR ACTIONS

Prostaglandins

PGI_2 (Prostacyclin): unstable; measured by its stable hydrolysis product 6-Keto PGF_1 : vasodilator and platelet antiaggregator

PGE_2: Formed and released on sympathetic nerve stimulation. Inhibits sympathetic transmission. May modulate sympathetic neuroeffector transmission; variable effects on CBF; potent anticonvulsant action; sedative; stimulates cyclic AMP. ? coregulator of adrenergic and dopaminergic pathways.

PGD_2: depresses sympathetic neurotransmission

PGF_2: hypothalamic secretion; anticonvulsant effect; reduces CBF

Thromboxane (TxA_2): unstable; measured by its stable hydrolysis product TxB_2: potent vasopressor, contracts respiratory smooth muscle, induces platelet aggregation.

Because trauma disruptive to cells and capillaries, in general, initiates the release of PGs, we hypothesized that missile injury to the brain would also be associated with release of polyunsaturated fatty acids and PGs. Ascertaining an increase in PGs might have important ramifications because PG increases have been associated with cerebral edema, altered blood flow and changes in brain function.

In conjunction with Dr. Giora Feuerstein at the Uniformed Services University of the Health Sciences in Bethesda, MD, we studied cyclooxygenase products of the brain itself and cerebrospinal fluid (CSF) to determine whether significant changes occurred in arachidonic acid metabolism following missile injury.

Method: We obtained blood, CSF, and brain specimens for PG and thromboxane determinations in control and wounded cats 5 minutes, 1 hour and 24 hours after anesthesia and surgery (controls) or after anesthesia, surgery and brain wounding (experimental cats). Each control or experimental group was comprised of from 3 to 7 animals.

We obtained arterial blood just prior to sacrifice for TxB_2 measurements from an indwelling arterial line. After withdrawal, we immediately placed 1.2ml of whole blood into a test tube containing 12 ul of indomethacin in a solution of 0.1m NaOH, pH 9.0. After centrifugation we separated the plasma and placed it in a -70°C deep freeze.

We also obtained 1 to 2ml of CSF from the cisterna magna of control and wounded cats just prior to sacrifice. The CSF samples were immediately frozen in dry ice and then placed in a -70°C freezer. Care was taken to insure that all CSF samples were relatively bloodless.

After CSF and blood samples had been obtained, the cats were exsanguinated and decapitated. We quickly removed the brains, sliced them, and placed each brain slice on a slab of dry ice. Samples of frozen brain adjacent to the missile track were removed, placed in containers and then placed in a -70°C deep freeze prior to being sent to Dr. Feuerstein.

All samples were sent packed in dry ice to Dr. Feuerstein's laboratory in Bethesda where analyses for PGs and thromboxane were performed by Dr. Esther Shohami.

Tissue samples were prepared as follows:

CSF: 0.1 ml of unpurified CSF was used for each radioimmunoassay determination.

Brain tissue: aliquots of brain tissue homogenates (1:10 ice cold tris-EDTA buffer) were taken for protein determination (55). Following centrifugation, the supernatants were washed 3 times with ether (96-98%)* and 0.1 ml of the aqueous phase used for each radioimmunoassay.

Plasma: 0.1 ml aliquots of the prepared plasma samples were used for plasma TxB_2 determinations by means of commerically available radioimmunoassay kits.**

CSF and brain samples plus standards*** were incubated for 18-24 hours at 4°C in highly specific antisera (for 6-keto PGF 1 , PGE_2, PGD_2 and TxB_2) along with tritiated radioligand**** (100-200 uCi/mmol). All radioimmunoassays were performed in 0.1% bovine serum albumin (56). Separation of bound and free fractions was achieved by dextran coated charcoal (Norit-SG, Activated)***** Radioactivity of each speciman was measured by scintillation counting. Data were analyzed by ANOVA followed by Newman-Keul's test for specific comparisons.

RESULTS

The concentrations of 6-Keto-PGF_1 (prostacyclin), TxB_2 (thromboxane), PGE_2, and PGD_2 in CSF and brain at 5 minutes, 60 minutes and 24 hours after wounding are shown in tables 15-17. Only TxB_2 was assayed in the plasma samples, table 18.

We could not detect significant changes in any cyclooxygenase products in the brain adjacent to the missile track when compared to the non-wounded, hemisphere and to control animals. However, large and highly significant ($p<0.001$) rises in all measured PGs were detectable in the CSF within 5 minutes of wounding. These sharp increases subsequently decreased towards control levels at 24 hours, figures 35-38. A suggestive rise in plasma TXB_2 was apparent 1 hour following injury, table 18.

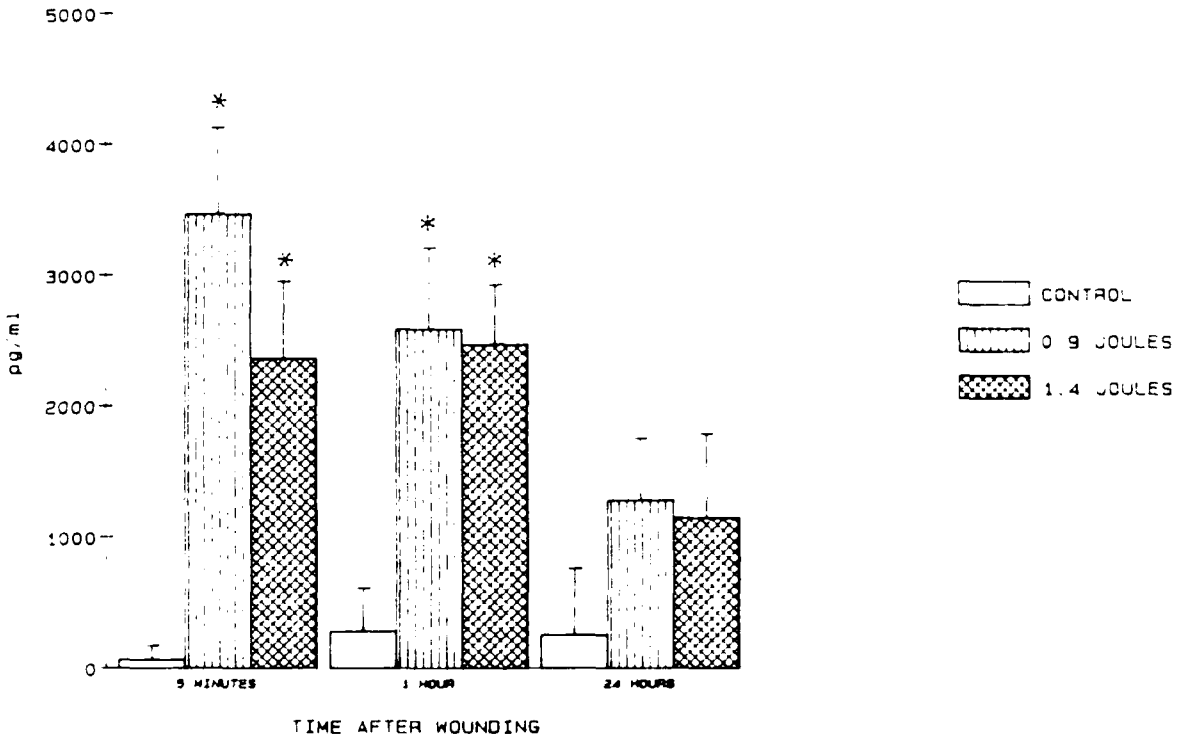
* Mallinckrodt Chemical Works, St. Louis, MO, 63160
** New England Nuclear, Boston, MA, 02118
*** Obtained from Dr. L. Levine, Brandeis, University, Waltham, MA 02254 (54)
**** New England Nuclear, Boston, MA, 02118
***** Sigma Chemical Company, St. Louis, MO, 63178

Table 15: PROSTAGLANDIN LEVELS IN CSF AT 5 MINUTES 1 HOUR, AND 24 HOURS AFTER A RIGHT HEMISPHERE WOUND BY A 0.9 OR A 1.4 JOULE MISSILE (pg/ml)

Time		(Prostacyclin) 6 Keto $PGF_{1\alpha}$	(Thromboxane) TxB_2	PGE_2	PGD_2
	control	63 ± 109(3)	510 ± 458(3)	519 ± 41(3)	429 ± 684(3)
5min	0.9J	3467 ± 662(4)*	3498 ± 105(4)*	4178 ± 443(4)*	4222 ± 1063(4)*
	1.4J	2364 ± 586(2)*	4000 ± 370(2)*	7192 ± 2822(2)*	4429 ± 1896(2)*
	control	279 ± 330(5)	73 ± 100(5)	599 ± 179(5)	238 ± 475(4)
1hr	0.9J	2586 ± 626(6)*	2052 ± 342(6)*	2738 ± 633(6)*	616 ± 802(6)
	1.4J	2466 ± 458(2)*	2357 ± 8(2)*	6010 ± 940(2)*	423 ± 345(2)
	control	252 ± 505(4)	55 ± 110(4)	238 ± 76(4)	200 ± 364(4)
24hrs	0.9J	1278 ± 474(4)	11 ± 22(4)	1079 ± 606(4)	230 ± 367(4)
	1.4J	1148 ± 639(4)	0 (4)	818 ± 190(4)	81 ± 162(4)

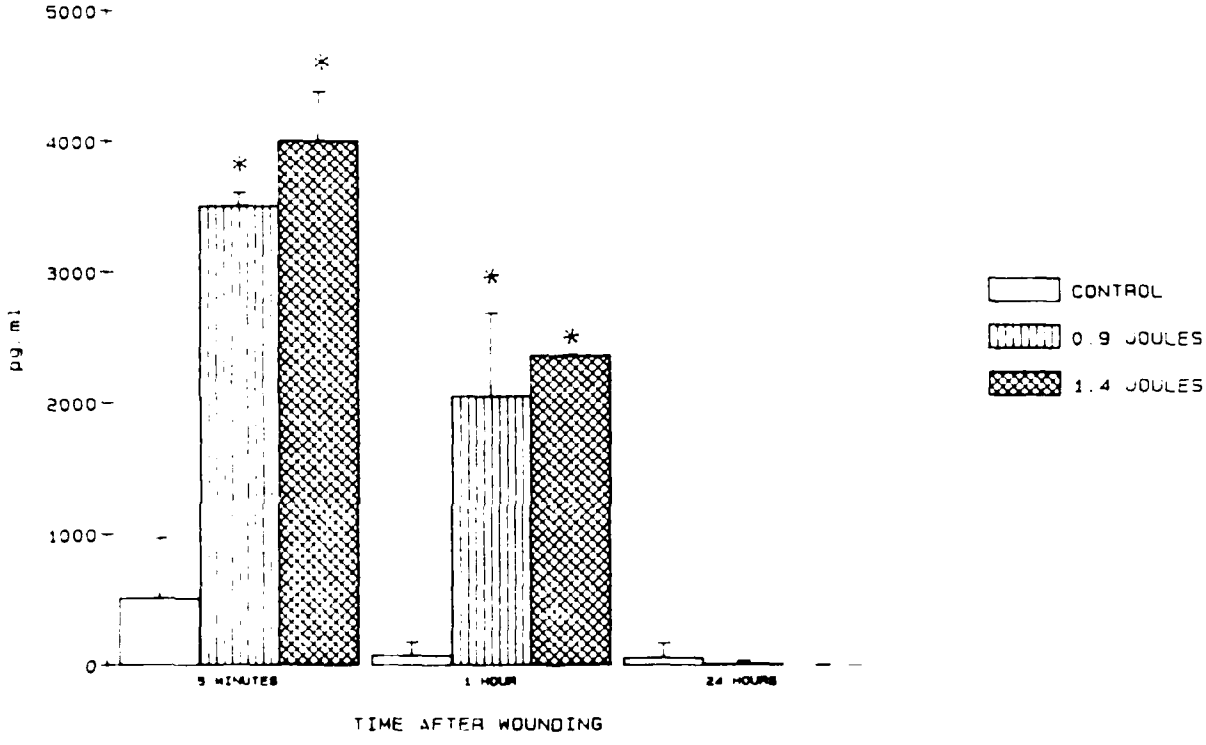
Data are the means ± SEM of (n) animals

* $p < 0.001$



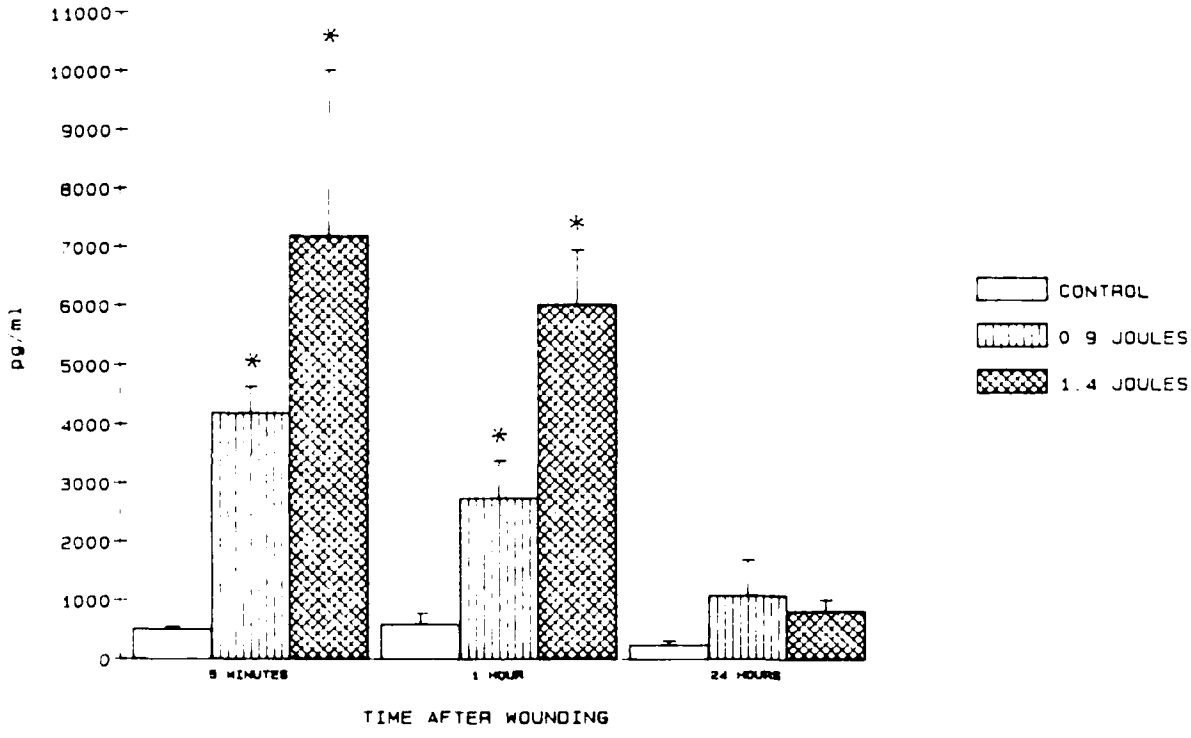
* $p < 0.001$

Figure 36: CSF prostacyclin ($PGF_{1\alpha}$) levels following wounding.



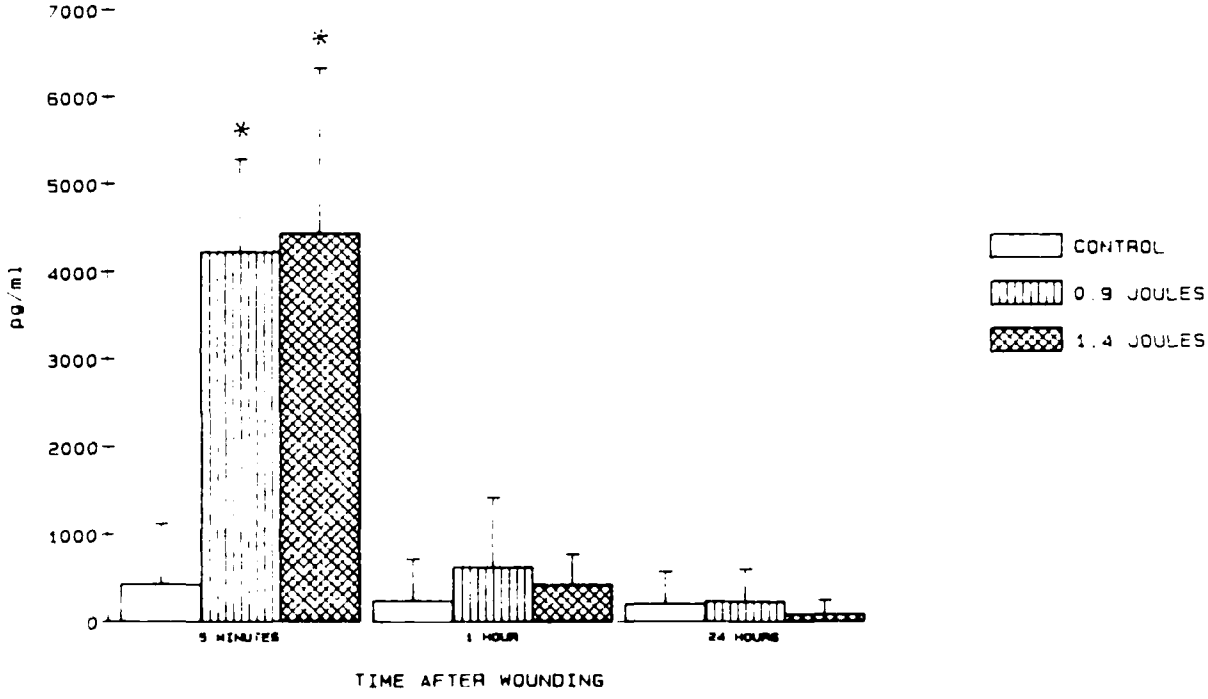
*p< 0.001

Figure 37: CSF thromboxane (TxB_2) levels following wounding.



*p< 0.001

Figure 38: CSF PGE_2 levels following wounding.



*p< 0.001

Figure 39: CSF PGD_2 levels following wounding.

Table 16: PROSTAGLANDIN LEVELS IN THE RIGHT (WOUNDED) HEMISPHERE AT 5 MINUTES, 1 HOUR, AND 24 HOURS AFTER WOUNDING BY A 0.9 OR A 1.4 JOULE JOULE MISSILE (pg/mg)

Time		(Prostacyclin) 6-Keto $PGF_{1\alpha}$	(Thromboxane) TxB_2	TxB_2/F_1	PGE_2
	control	1290 ± 164(4)	157 ± 18(4)	0.127 ± 0.019(4)	594 ± 110(4)
5min	0.9J	890 ± 186(4)	194 ± 59(4)	0.212 ± 0.028(4)	473 ± 209(3)
	1.4J	972 ± 155(4)	155 ± 29(4)	0.157 ± 0.015(4)	516 ± 139(4)
	control	1310 ± 380(4)	153 ± 51(4)	0.111 ± 0.012(4)	412 ± 93(4)
1hr	0.9J	887 ± 118(7)	199 ± 24(7)	0.241 ± 0.038(7)	429 ± 56(7)
	1.4J	1188 ± 284(3)	320 ± 74(3)	0.300 ± 0.105(3)	696 ± 288(3)
	control	1359 ± 292(4)	185 ± 54(4)	0.131 ± 0.015(4)	596 ± 173(4)
24hrs	0.9J	1044 ± 185(6)	130 ± 29(6)	0.123 ± 0.010(6)	388 ± 105(6)
	1.4J	1328 ± 352(4)	122 ± 34(5)	0.098 ± 0.003(4)	353 ± 107(5)

Data are the means ± SEM of (n) animals

Table 17: PROSTAGLANDIN LEVELS IN THE LEFT (UNWOUNDED) HEMISPHERE AT 5 MINUTES, 1 HOUR, AND 24 HOURS AFTER WOUNDING BY A 0.9 OR A 1.4 JOULE MISSILE (pg/mg)

Time		(Prostacyclin) 6-Keto $PGF_{1\alpha}$	(Thromboxane) TxB_2	TxB_2/F_2	PGE_2
	control	686 ± 142(5)	136 ± 27(4)	0.202 ± 0.026(4)	557 ± 309(4)
5min	0.9J	1220 ± 309(5)	153 ± 73(4)	0.159 ± 0.046(4)	551 ± 186(4)
	1.4J	603 ± 176(3)	149 ± 36(4)	0.207 ± 0.038(3)	466 ± 207(4)
	control	978 ± 158(5)	158 ± 34(5)	0.158 ± 0.016(5)	994 ± 379(4)
1hr	0.9J	947 ± 223(7)	166 ± 25(7)	0.190 ± 0.013(7)	467 ± 98(7)
	1.4J	815 ± 106(3)	134 ± 41(3)	0.169 ± 0.049(3)	581 ± 222(3)
	control	1157 ± 186(3)	181 ± 40(3)	0.152 ± 0.013(3)	700 ± 365(3)
24hrs	0.9J	772 ± 129(5)	146 ± 31(4)	0.195 ± 0.018(4)	559 ± 153(6)
	1.4J	1254 ± 152(5)	177 ± 31 (5)	0.151 ± 0.029(5)	786 ± 109(5)

Data are the means ± SEM of (n) animals

Table 18: TxB_2 LEVELS IN PLASMA AT 5 MINUTES, 1 HOUR AND 24 HOURS AFTER WOUNDING BY A 0.9 OR A 1.4 JOULE MISSILE (pg/ml)

		(Thromboxane) TxB_2
	control	16 ± 19(4)
5 min	0.9J	11 ± 14(4)
	1.4J	40 ± 69(3)
	control	4 ± 8(5)
1 hour	0.9J	156 ± 105(7)
	1.4J	198 ± 327(3)
	control	76 ± 89(4)
24 hours	0.9J	11 ± 22(4)
	1.4J	0 (4)

Data are the means ± SEM of (n) animals

Discussion: Measurements of brain PGs may prove difficult even in normal animals because tissue PGs can be artificially elevated owing to their rapid synthesis following decapitation and before freezing. This process itself subjects brain cells to ischemia. This difficulty notwithstanding, a number of previous studies have shown that besides ischemia (57), concussive damage (58) and freeze lesions (59) also increase brain PG synthesis. Increased tissue PGs may produce secondary, additive damage to the brain owing to the biological activity of the various PGs by causing ischemia or by acting directly on brain neurons themselves.

In our cats, even among controls, brain PG levels were higher than would be expected owing, no doubt, to in situ PG synthesis following decapitation.(60) We felt it surprising that even higher PG levels were not found adjacent to the missile track because damaged cerebral vessels form PGI_2 (6 keto PGF_1) and platelets associated with intracerebral bleeding release thromboxane (TxB_2). Perhaps increases in tissue PGs resulting from wounding were masked by the generalized PG increase in the brain following decapitation and before freezing. If this were true, these data would tend to underestimate PGs formed adjacent to the missile track. Our data does suggest, however, that brain tissue thromboxane was increased one hour after wounding, table 16. Possibly, blood vessel vasoconstriction adjacent to the missile track and brain tissue ischemia about the wound might occur at this time. Neither brain tissue PGI_2 (6 ketoPGF_1) nor PGE_2 showed any tendency to increase in the brain after wounding which suggests that any increase in brain thromboxane (TxB_2) which occurred after wounding was preferential; (i.e. thromboxane was preferentially synthesized).

We have ascertained for the first time that brain missile wounding is associated with extremely large increase in CSF PGs. Again, because of their extremely active biological potential, these PGs could cause additional injury to the brain through vasoconstrictive effects and ischemia or by acting directly upon neurons. The source of these CSF PGs is unknown. They could arise from: (a) seepage of intraparenchymal PGs into the brain extracellular space and then into the CSF owing to the "sink action" of the CSF, (b) decreased PG efflux from CSF owing to saturation of carrier mediated PG transfer or receptor block, (c) blood elements in the CSF secondary to the missile trauma. This latter source is unlikely, however, because PGs in slightly bloody CSF samples were not higher than in CSF samples that were bloodless.

The rise in plasma TxB_2 in several animals is intriguing but owing to the high standard errors these data are only suggestive. One may speculate that thromboxane was carried from CSF to blood by chorcid plexus transport mechanisms.(61) The resulting increases in plasma thromboxane might contribute to neurogenic pulmonary edema because it has been shown that prostaglandins may cause pulmonary venous constriction.(62)

13. SUMMARY OF PHYSIOLOGIC FINDINGS:

This research project is the first of its kind where missile injury to the brain has been created through an intact skull and wounded animals have been followed for many days after wounding. This unique study has allowed us to ascertain for the first time certain pathophysiologic effects associated with brain wounding and relate them to overall animal behavior. By means of these experiments we make the following observations:

1) Non-fatal brain wounds caused by missiles involve a narrow band of missile energy. In our model 0.7 Joules was required to achieve skull penetration. A brain wound caused by 2.4 Joules was uniformly fatal from instantaneous and permanent respiratory arrest.

2) A serious brain wound of the cerebral hemisphere may be associated with considerable brainstem effects, most importantly involving "central" respiratory centers which may cause death by respiratory arrest. In our model this "indirect effect" of the right cerebral hemisphere wound upon medullary respiratory centers was energy dependent: increasing amounts of apnea occurred with increasing missile energy. Missile-induced apnea would have been fatal in many instances but with respiratory support we ascertained that 92% of cats eventually resumed spontaneous respirations and went on to live. THIS HAS VERY IMPORTANT CLINICAL IMPLICATIONS: POSSIBLY, TEMPORARY RESPIRATORY SUPPORT MIGHT SAVE INDIVIDUALS WHO HAVE SUSTAINED BRAIN WOUNDS WHICH ORDINARILY WOULD KILL BY CAUSING PROLONGED APNEA.

3) Intracranial pressure undergoes a sustained rise and cerebral perfusion pressure a sustained fall after missile injury. The magnitude of these changes is proportional to missile energy. Fatal brain wounds are associated with marked cerebral perfusion pressure reductions.

4) Brain wounding may cause pulmonary function changes ranging from mild increases in arterial pCO_2, and mild decreases in arterial pH and pO_2 to frank, fatal neurogenic pulmonary edema.

5) Brainstem effects determine whether the brain-wounded animal will live or die; cortical damage (interacting with subcortical centers) determines long-term neurologic residua. Focal neurologic deficits induced by a missile wound tend to improve in time; e.g. in our model contralateral hemiparesis tended to disappear in about 7 days.

6) Brain wounding is associated with breakdown in the blood-brain barrier and vasogenic brain edema which occurs predominately about the missile track. In our model the vasogenic brain edema became significant at 24 hours, peaked at 24-48 hours, and then began to recede without any treatment whatsoever. It was not life threatening. Neurologic deficits after wounding did not correlate with the presence of cerebral edema. Blood-brain barrier breakdown occurred in the brainstem without measurable brainstem edema.

7) Missile wounding is associated with extremely large increases in CSF prostaglandins measureable within minutes of wounding. Prostaglandins are biologically very active and, conceivably, might further degrade neural function either directly or by causing cerebral ischemia.

Figures 40-43 summarize the acute and subacute physiologic events which we have thus far determined to be associated with a missile wound to the brain. For data presentation physiologic events associated with a 1.4 Joule missile wound are summarized. Unless otherwise stated these data represent averages from five animals.

Figure 40

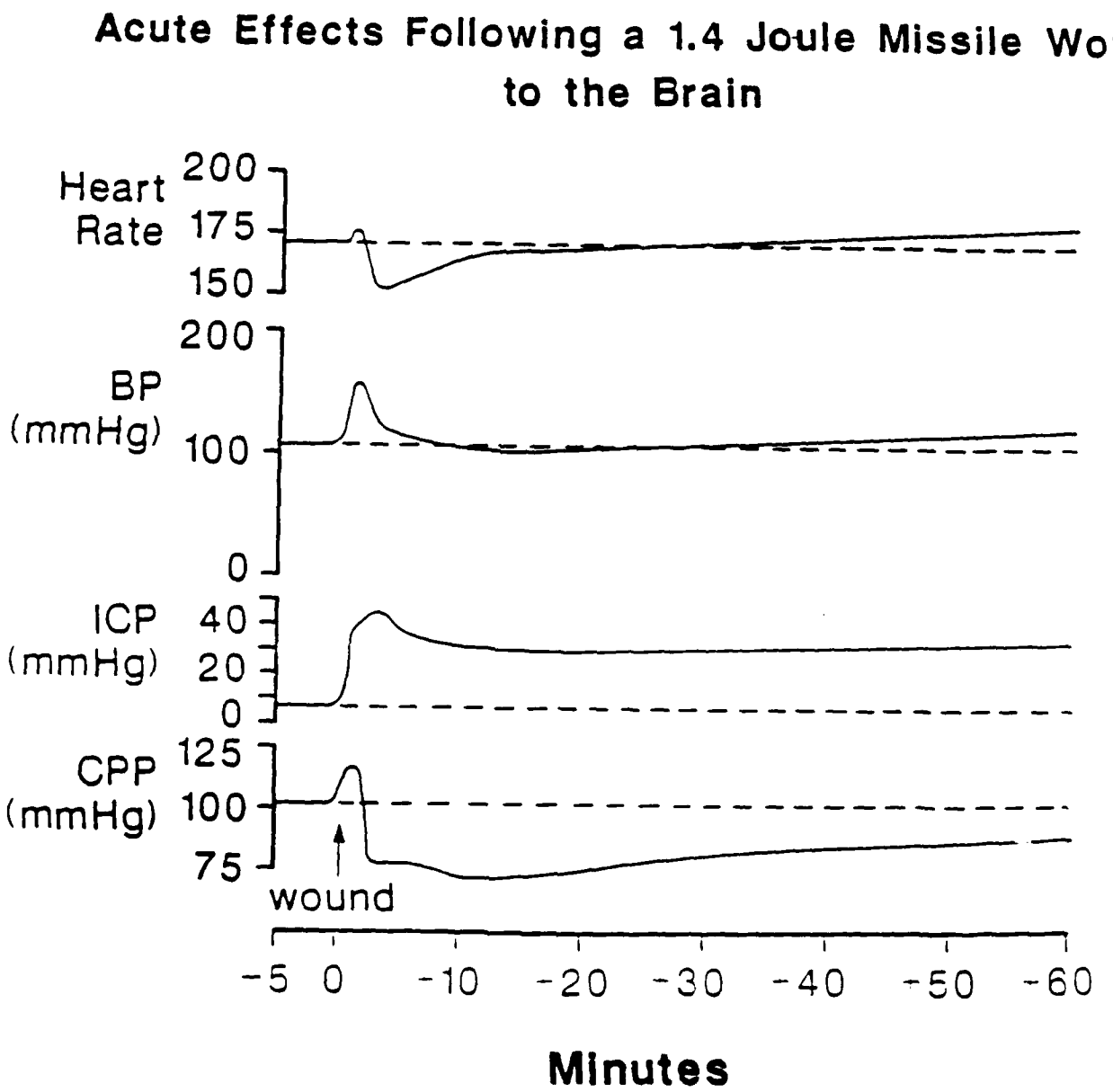


Figure 41

Acute Effects Following a 1.4 Joule Missile Wound to the Brain

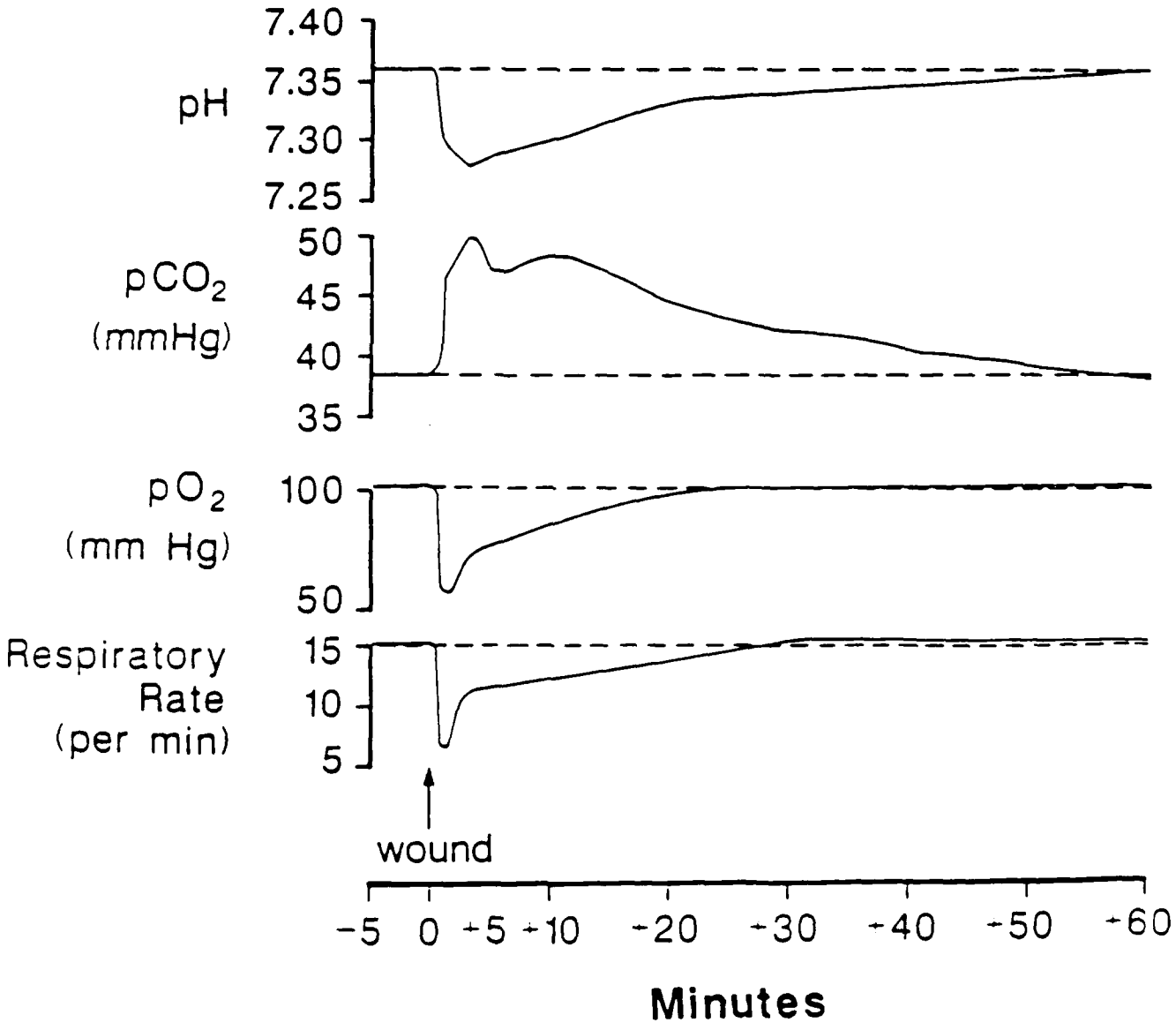


Figure 42

Acute Effects Following a 1.4 Joule Missile Wound to the Brain

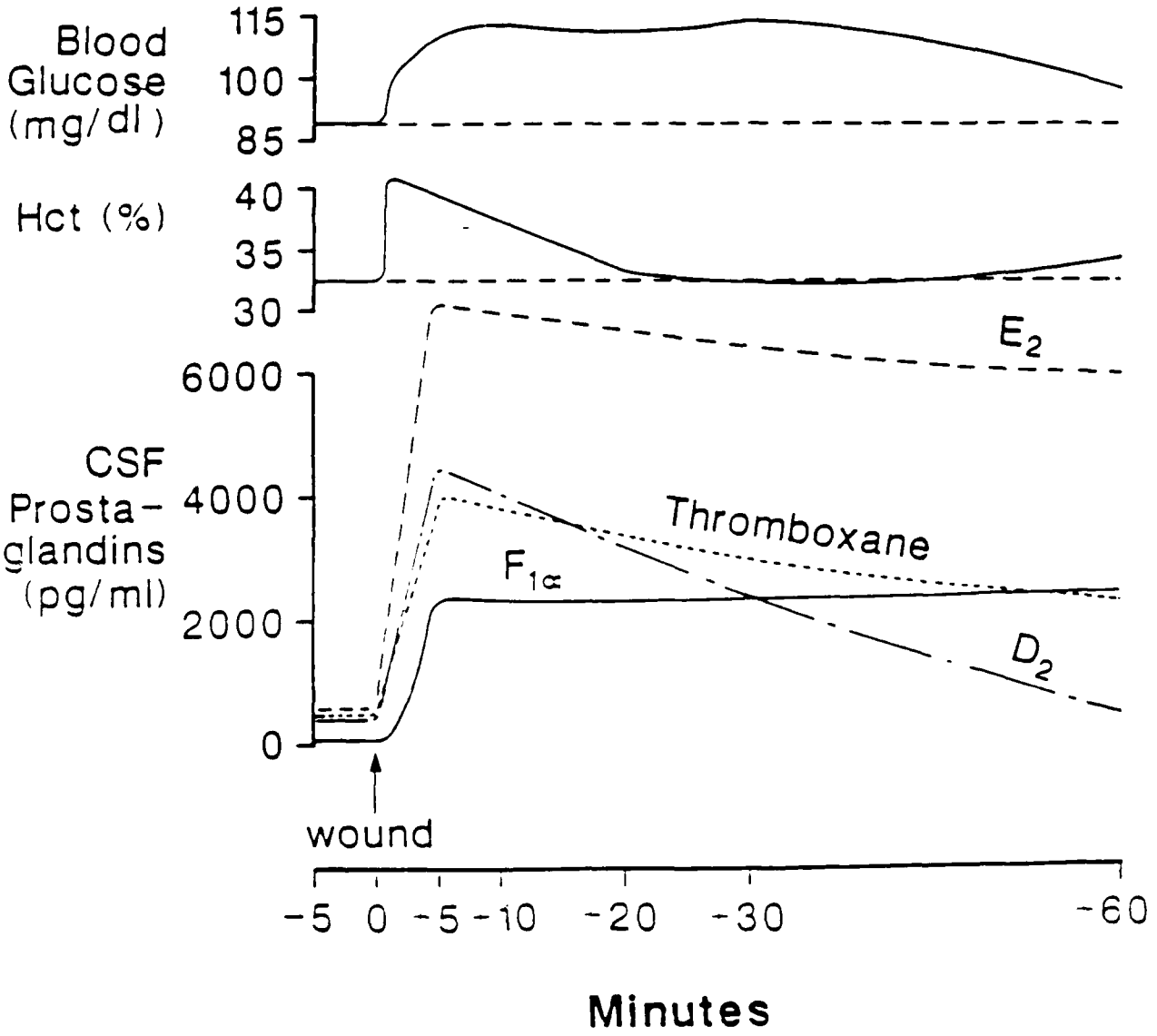
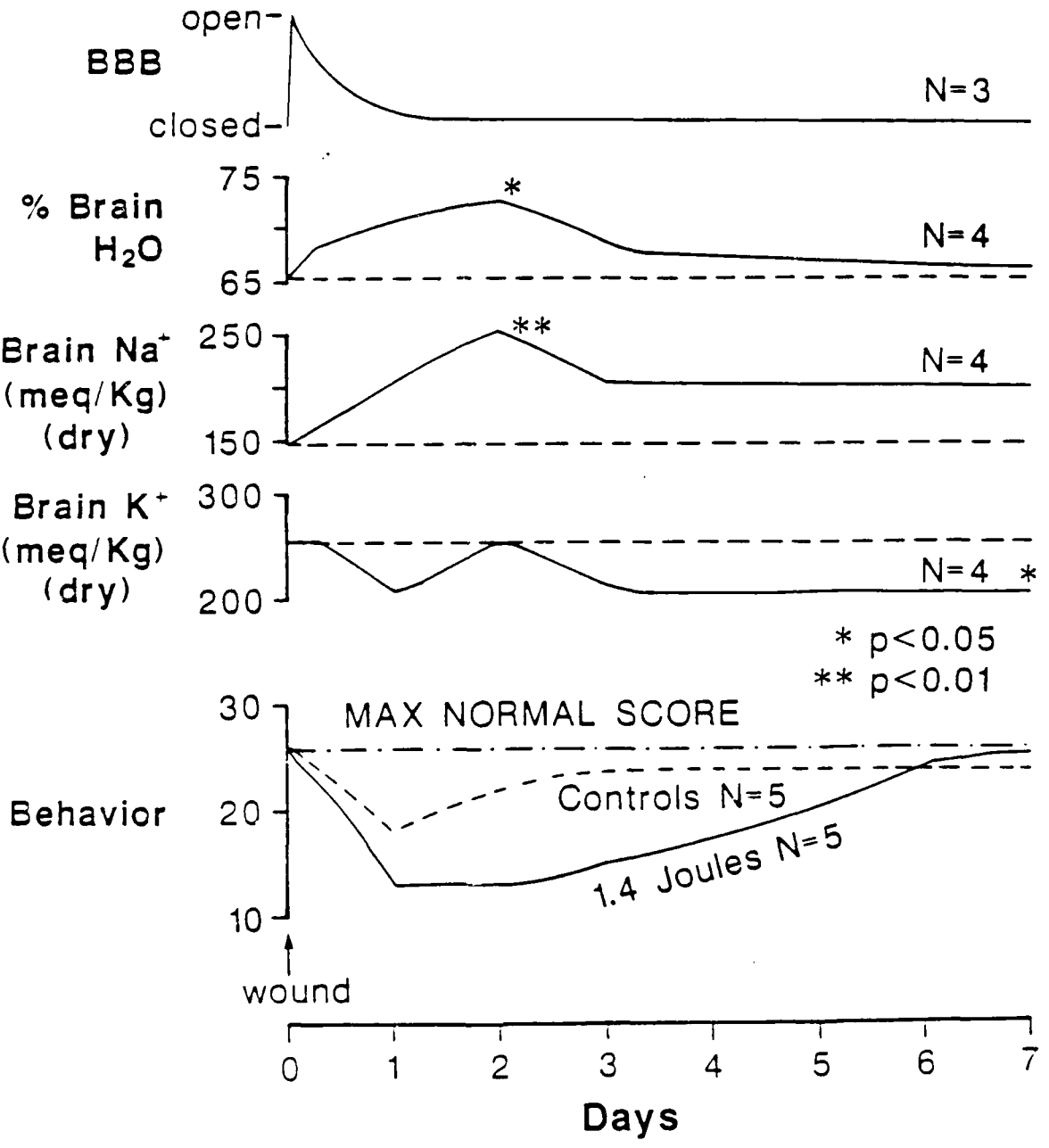


Figure 43

Subacute Effects of a 1.4 Joule Missile Wound to the Brain



14. CONCLUSIONS:

1) A missile wound to the cerebral hemispheres often affects the brainstem and causes spontaneous respirations to cease. Death from a severe missile wound to the brain, therefore, may often result from respiratory arrest rather than from intrinsically fatal brain damage. Our experiments have shown that the respiratory arrest may be reversible and spontaneous respirations may resume provided ventilatory support is given. HENCE, MORTALITY FROM BRAIN WOUNDING MIGHT BE REDUCED IN MANY WHO RECEIVE BRAIN WOUNDS IF RESPIRATORY SUPPORT WERE GIVEN IMMEDIATELY AFTER WOUNDING. Brain missile wounding may also affect lung function per se.

2) A missile wound to the brain produces vasogenic brain edema primarily in the white matter of the wounded cerebral hemisphere. This edema appears to be mild and self limited, probably because the blood-brain barrier closes 24 to 48 hours after wounding.

3) Very substantial rises in CSF prostaglandins occur immeidately after wounding. These prostaglandins could secondarily damage the brain directly by damaging neurons or indirectly by causing vasoconstriction and ischemia about the wounded brain.

4) We have developed a laboratory model whereby drugs which might improve brainstem or cortical dysfunction after missile wounding can be tested. If drugs are found which improve brain function after injury, mortality and morbidity after brain wounding may be reduced.

15. RECOMMENDATIONS:

1) Further investigations are needed to ascertain the nature of the brainstem damage which results in apnea after a missile wound to the brain. TREATMENT OF THIS BRAINSTEM DYSFUNCTION MAY DRAMATICALLY DECREASE THE MORTALITY ASSOCIATED WITH BRAIN WOUNDS.

2) We should determine whether superimposed ischemia, hypoxia or hypercarbia increases the amount brain edema seen after missile wounding. If so, this would indicate that soldiers who receive a brain wound plus any of these other metabolic insults would be at increased risk of incurring more deleterious brain swelling than usual. They may require special treatment beyond that usually needed for a brain wound.

3) We should begin evaluating drugs which might improve brainstem and/or cortical function after a brain wound. These drugs can be selected from those which have shown promise in other experimental models.

4) We should continue characterizing the nature of the physiological and biochemical abnormalities which occur after missile wounding because VIRTUALLY NONE OF THESE DETAILS ARE KNOWN. Ascertaining thse abnormalities will provide the most rational basis for the selection of drugs to improve brain function after wounding.

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APPENDIX

PHYSIOLOGIC DATA-CONTROLS, 5 ANIMALS
(X ± SD)

	cont	1min	3min	5min	10min	20min	30min	60min
BP	97.0 ±10.0	99.8 ±5.7	100.0 ±6.0	102.6 ±7.1	107.4 ±9.7	115.4 ±14.2	115.4 ±11.7	120.8 ±15.0
ICP	6.7 ±2.5	64. ±2.8	6.6 ±1.9	6.7 ±2.1	6.8 2.0	6.5 ±2.1	6.6 ±2.3	7.2 ±3.3
CPP	90.3 ±9.5	93.4 ±5.6	93.4 ±6.1	95.9 ±7.0	100.6 ±8.7	108.9 ±13.1	108.6 ±11.4	113.6 ±14.6
pH	7.34 ±0.05	7.33 ±0.05	7.32 ±0.06	7.34 ±0.06	7.33 ±0.04	7.34 ±0.04	7.35 ±0.03	7.37 ±0.02
pCO_2	40.7 ±5.5	42.3 ±6.1	43.1 ±1.9	44.3 ±3.9	41.0 ±4.7	41.7 ±4.6	41.6 ±5.1	38.3 ±3.9
pO_2	88.8 ±15.8	89.5 ±17.8	90.5 ±16.4	93.2 ±13.8	92.3 ±16.5	99.0 ±17.2	97.5 ±20.3	105.0 ±18.3
HR	160.8 ±11.5	159.6 ±10.0	160.8 ±11.5	162.0 ±16.4	164.4 ±14.4	164.4 ±19.3	163.2 ±19.6	165.6 ±28.3
Resp	14.2 ±4.0	13.0 ±3.3	13.0 ±3.9	13.4 ±3.6	13.8 ±4.9	14.4 ±5.5	14.6 ±5.5	14.8 ±5.4
Glu	89.4 ±18.8	97.2 ±10.7	95.0 ±19.0	97.4 ±15.4	91.2 ±18.0	93.6 ±19.5	109.6 ±29.2	111.8 ±26.7
Hct	26.4 ±1.5	27.2 ±1.3	27.0 ±1.2	26.8 ±1.3	26.9 ±1.5	27.2 ±2.6	27.2 ±2.8	26.2 ±1.6

Appendix Table 19: Summary of physiologic data on 5 control, anesthetized unwounded cats during the first 70 minutes in which they were in the stereotaxic frame. Note: This table gives X ± SD; the corresponding graphs show X ± SE.

PHYSIOLOGIC DATA -5 ANIMALS WOUNDED AT 0.9 JOULES
(X ± SD)

	cont	1min	3min	5min	10min	20min	30min	60min
BP	111.2 ±24.7	164.2 ±44.7	121.6 ±26.1	112.0 ±32.5	112.8 ±32.9	112.3 ±30.3	114.4 ±30.1	125.3 ±22.8
ICP	8.8 ±4.8	24.6 ±13.2	22.0 ±9.4	19.2 ±6.8	17.6 ±7.2	20.2 ±10.8	20.9 ±12.5	17.6 ±9.0
CPP	102.4 ±21.9	139.6 ±38.5	99.6 ±21.2	92.8 ±29.5	95.2 ±28.7	92.1 ±25.7	93.5 ±25.8	107.7 ±22.8
pH	7.37 ±0.07	7.34 ±0.05	7.33 ±0.07	7.34 ±0.06	7.35 ±0.05	7.37 ±0.06	7.38 ±0.06	7.39 ±0.07
pCO_2	39.8 ±5.5	38.4 ±8.6	46.9 ±15.7	40.7 ±7.6	37.2 ±8.3	38.1 ±11.7	36.7 ±11.3	34.9 ±7.6
pO_2	89.9 ±10.6	86.5 ±32.2	87.4 ±19.8	89.8 ±13.5	102.0 ±23.3	101.3 17.3	107.3 ±25.2	103.4 ±12.7
HR	195.6 ±16.2	186.4 ±36.3	174.0 ±27.5	181.2 ±25.9	188.4 ±27.0	198.0 ±20.8	200.4 ±18.3	198.0 ±28.1
Resp	13.6 ±3.8	8.0 ±9.0	15.6 ±8.0	16.0 ±8.7	14.2 ±5.3	14.6 ±5.4	16.0 ±6.1	19.6 ±8.7
Glu	87.6 ±31.1	98.4 47.7	119.0 ±54.3	124.8 ±49.3	137.8 ±46.4	127.8 ±56.7	126.2 ±58.2	148.0 ±71.7
Hct	31.6 ±4.9	38.9 ±6.9	38.5 ±7.0	37.6 ±6.3	35.2 ±5.0	34.4 ±2.8	33.5 ±3.3	34.3 ±2.8

Appendix Table 20: Summary of physiologic data on 5 anesthesized cats wounded at 0.9 Joules. Values are for a control period shortly before wounding and 7 subsequent times up to 60 minutes after wounding. Note: this table gives X ± SD; the corresponding graphs show X ± SE.

PHYSIOLOGIC DATA-5 ANIMALS WOUNDED AT 1.4 JOULES
(X ± S.D.)

	cont	1min	3min	5min	10min	20min	30min	60min
BP	108.5 ±8.8	154.5 ±31.8	122.7 ±17.9	113.4 ±15.6	101.7 ±7.4	104.0 ±28.1	110.0 ±25.6	121.5 ±16.8
ICP	6.6 ±2.9	36.8 ±24.0	45.0 ±25.2	35.8 ±21.7	30.2 ±16.4	29.0 ±8.9	28.8 ±7 7	33.8 ±19.8
CPP	101.9 ±9.0	117.7 ±28.2	77.7 ±21.9	77.6 ±7.8	71.5 ±17.5	75.0 ±34.5	81.2 ±31.1	87.7 ±16.4
pH	7.36 ±0.05	7.30 ±0.05	7.28 ±0.04	7.29 ±0.04	7.30 ±0.06	7.33 ±0.06	7.34 ±0.07	7.36 ±0.08
pCO_2	38.4 ±5.0	46.6 ±4.9	50.0 ±5.1	47.2 ±7.4	48.4 ±9.9	44.1 ±8.7	42.4 ±8.9	38.0 ±8.2
pO_2	102.1 ±16.2	55.7 12.7	74.7 ±3.5	81.3 ±9.2	88.6 ±9.8	98.7 ±8.6	103.2 ±10.4	103.6 ±14.8
HR	170.4 ±13.1	175.2 ±24.5	152.4 ±10.9	156.0 ±11.2	166.8 ±25.2	168.0 ±27.8	172.8 ±27.9	178.8 ±30.4
Resp	15.2 ±6.7	6.6 ±9.2	11.2 ±4.0	11.4 ±5.2	12.2 ±5.4	13.8 ±6	15.8 ±6.9	15.6 ±8.6
Glu	90.2 ±16.3	99.8 ±18.6	105.6 ±12.6	111.4 ±18.6	113.4 ±41.2	111 ±27.6	114.4 ±28.4	98.0 ±24.0
Hct	32.3 ±3.6	40.8 ±5.0	40.5 ±5.0	39.6 ±4.0	37.1 ±4.8	33.1 ±4.2	32.7 ±3.2	34.3 ±3.5

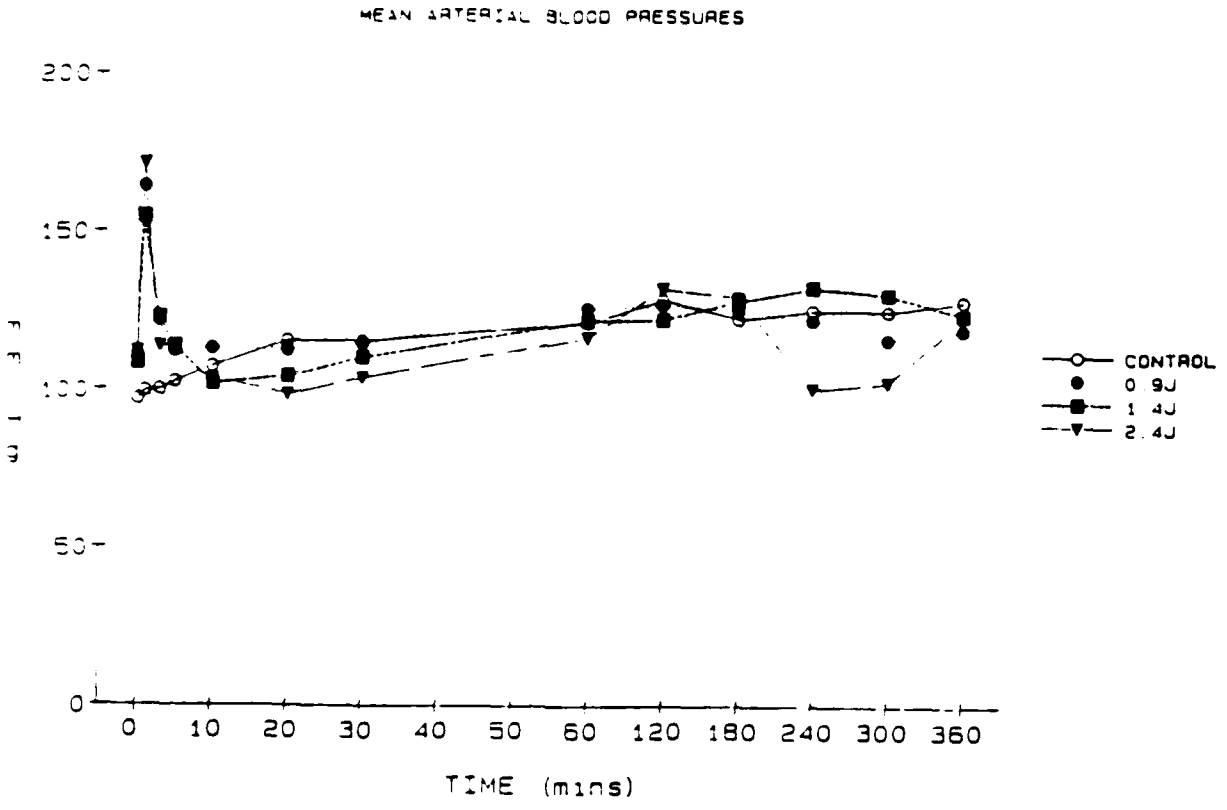
Appendix Table 21: Summary of physiologic data on 5 anesthetized cats wounded at 1.4 Joules. Values are for a control period shortly before wounding and 7 subsequent times up to 60 minutes after wounding. Note: this table gives X + SD; the corresponding graphs show X ± SE.

PHYSIOLOGIC DATA- 5 ANIMALS WOUNDED AT 2.4 JOULES
(X ± SD)

	cont	1min	3min	5min	10min	20min	30min	60min
BP	111.9 ±18.3	171.5 ±40.1	113.6 ±33.4	113.9 ±39.3	103.2 ±34.2	98.4 ±34.3	103.5 ±34.1	116.0 ±48.7
ICP	6.5 ±3.4	62.6 ±35.9	62.4 ±27.8	63.2 ±34.9	49.6 ±16.3	45.4 ±20.2	42.8 ±22.9	38.0 ±12.2
CPP	105.4 ±20.9	108.9 ±47.5	51.2 ±39.5	50.7 ±42.6	53.6 ±40.1	53.0 ±39.7	60.9 47.5	72.5 ±68.8
pH	7.35 ±0.04	7.33 ±0.04	7.32 ±0.06	7.29 ±0.05	7.34 ±0.08	7.35 ±0.10	7.35 ±0.07	7.36 ±0.05
pCO_2	41.0 ±4.9	43.6 ±8.9	46.6 ±9.6	48.9 ±5.7	44.1 ±9.8	42.3 ±10.2	41.9 ±7.4	39.7 ±5.6
pO_2	101.2 ±26.5	69.9 ±29.7	85.8 ±34.3	86.0 ±34.4	112.2 ±19.2	110.8 ±13.3	113.1 ±13.8	114.5 ±9.7
HR	180 ±18	171.6 ±16.2	151.2 ±5.0	160.8 ±14.3	164.4 ±13.1	172.8 ±27.6	175.2 ±32.7	183.6 ±40.6
Resp	13.0 ±1.7	9.4 ±7.8	15.0 ±10.2	14.2 ±0.4	14.0 ±7.3	14.6 ±6.9	15.0 ±5.6	15.6 ±8.3
Glu	85.6 ±21.4	87.2 ±17.6	107.8 ±40.3	113.0 ±46.5	135.6 ±67.5	141.4 ±60.6	131.4 ±50.3	128.2 ±58.6
Hct	32.8 ±2.9	40.5 ±4.9	39.5 ±4.1	38.9 ±4.1	36.9 ±3.5	33.8 ±4.3	33.5 ±4.0	34.0 ±3.2

Appendix Table 22: Summary of physiologic data on 5 anesthetized cats wounded at 2.4 Joules. Values are for a control period shortly before wounding and 7 subsequent times up to 60 minutes after wounding. Note: this table gives X ± SD; the corresponding graphs show X ± SE.

Figure 44: Mean arterial blood pressure (MABP) for controls and cats wounded at 0.9, 1.4 and 2.4 Joules.



Figures 45-48: Mean arterial blood pressure (MABP) controls and cats wounded at 0.9, 1.4, and 2.4 Joules. (means ± S.E. n=5)

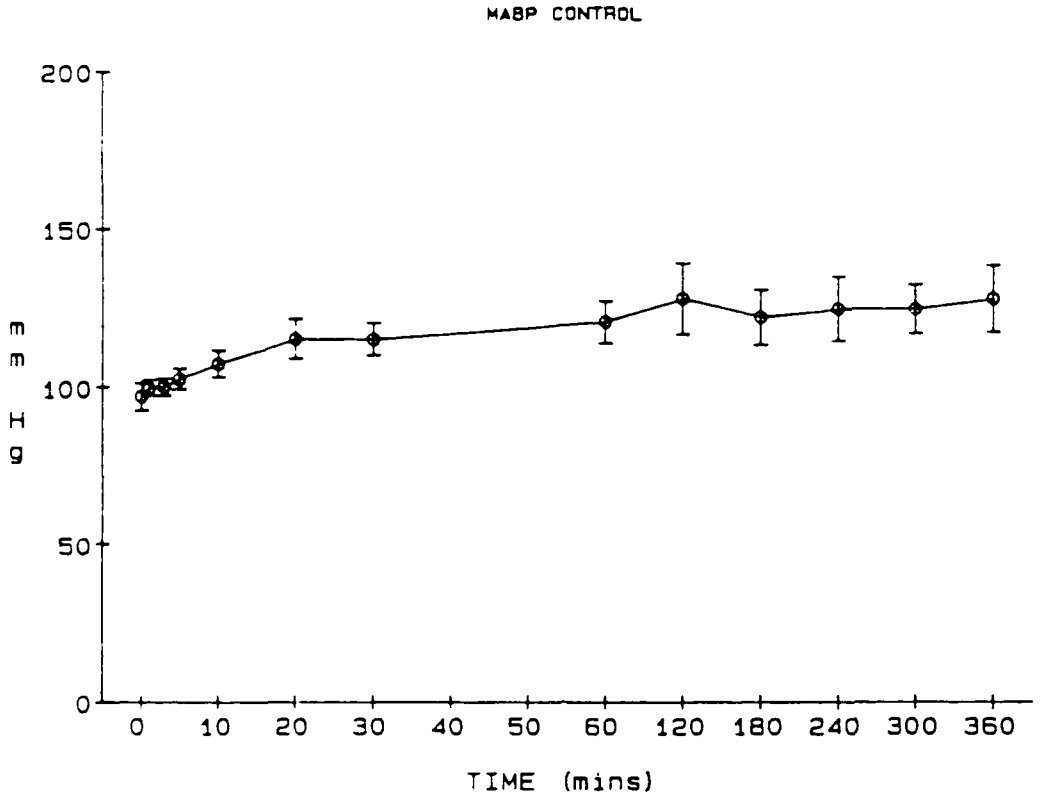


Figure 45

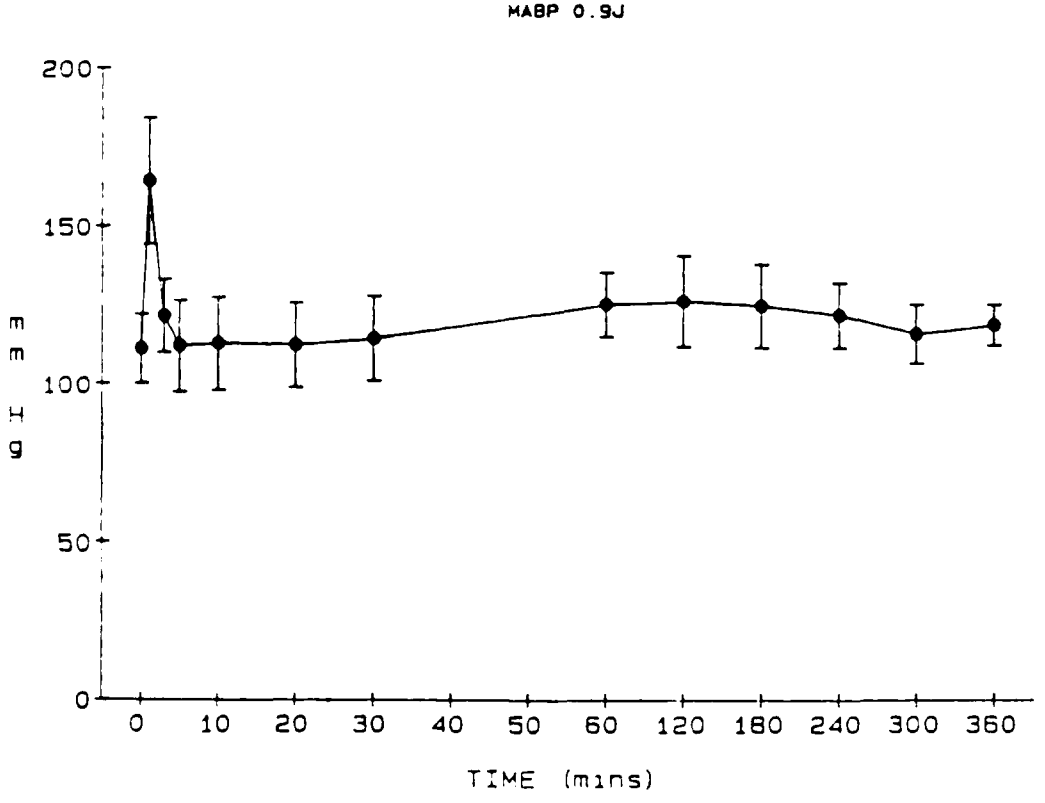


Figure 46

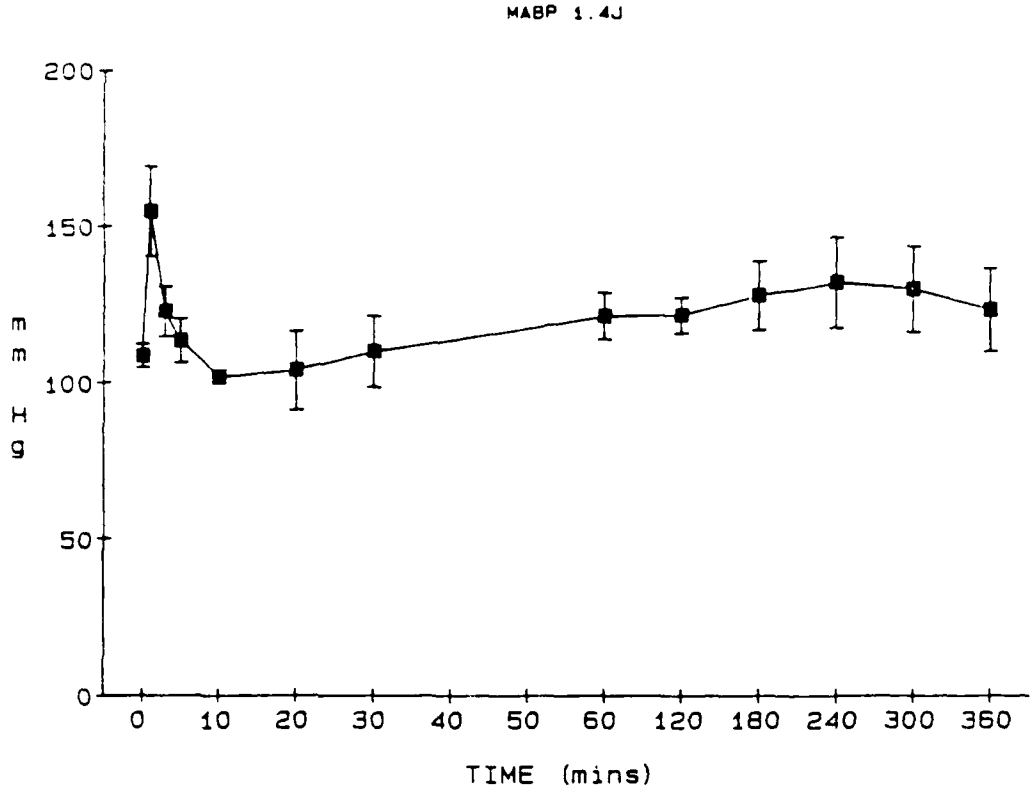
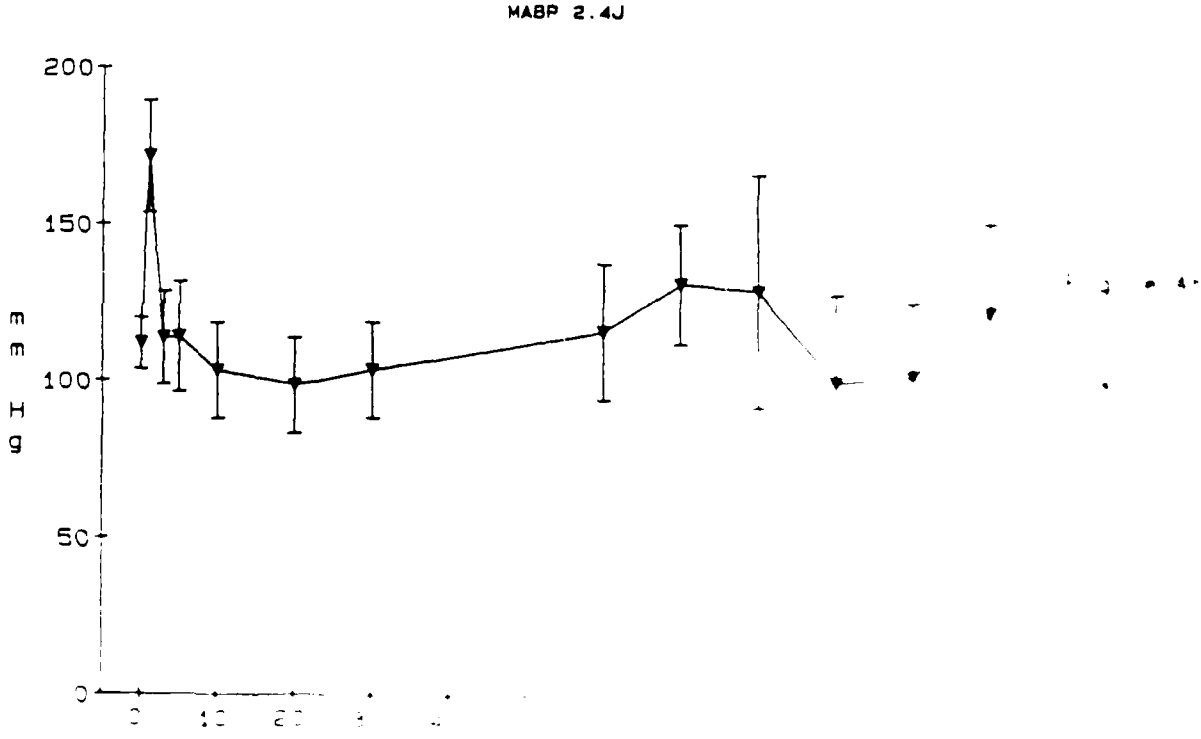

MABP 1.4J
200
150
100
50
0
mmHg
0
10
20
30
40
50
60
120
180
240
300
360
TIME (mins)
mABP

Figure 47


MABP 2.4J
200
150
100
50
0
mmHg

AD-A184 072 THE EFFECT OF AN EXPERIMENTAL MISSILE WOUND TO THE BRAIN ON BRAIN ELECTRO (U) LOUISIANA STATE UNIV MEDICAL CENTER NEW ORLEANS M E CAREY ET AL 10 FEB 87 2/2

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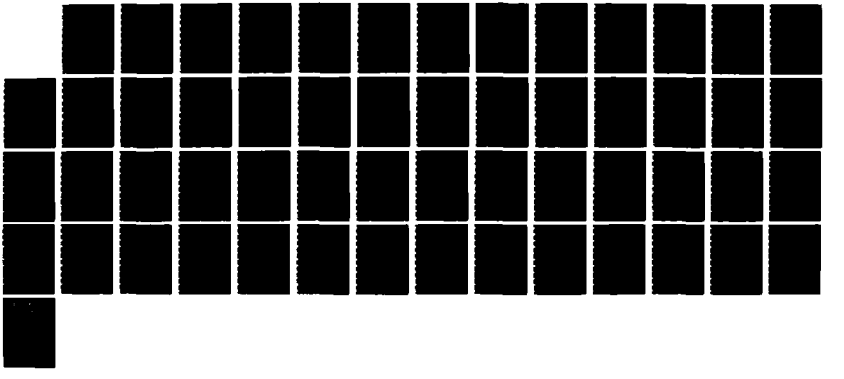


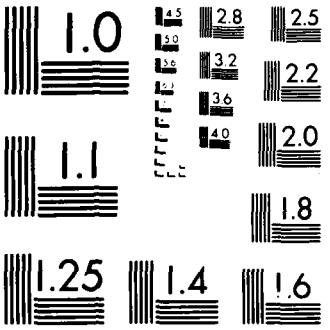


Table 23: Blood Pressure Controls

TIME	C261	C262	C263	C267	C269	MEANS	SD
0	112	92	92	102	87	97.0	10.000000
1	107	95	102	102	93	99.8	5.718391
3	107	98	92	105	98	100.0	6.041523
5	108	108	93	107	97	102.6	7.092249
10	123	103	98	103	110	107.4	9.710819
20	135	113	97	110	122	115.4	14.152738
30	128	110	98	117	123	115.2	11.734564
60	108	130	102	127	137	120.8	15.023315
120	103	102	130	153	153	128.2	25.272515
180	108	107	113	153	130	122.2	19.537144
240	105	110	110	150	150	125.0	22.912878
300	130	110	107	150	127	124.8	17.340704
360	110	115	108	160	147	128.0	23.864199

Table 24: Blood Pressure 0.9 Joules

TIME	M219	M227	M231	M233	M239	MEANS	SD
0	85.3	150.7	98.7	105.3	116.0	111.20	24.724280
1	150.3	209.3	132.0	213.3	116.0	164.18	44.716071
3	120.0	166.7	110.7	101.3	109.3	121.60	26.070865
5	88.0	165.3	108.0	84.0	114.7	112.00	32.496846
10	76.0	164.0	108.0	96.0	120.0	112.80	32.912004
20	80.0	158.7	110.7	92.0	120.0	112.28	30.291038
30	78.0	156.0	114.0	95.3	128.7	114.40	30.103903
60	107.3	160.0	110.7	111.3	137.3	125.32	22.810349
120	104.0	178.7	119.3	97.3	132.7	126.40	32.303096
180	98.0	170.7	108.0	110.0	137.3	124.80	29.506694
240	96.0	153.3	110.7	112.0	137.3	121.86	23.007455
300	100.0	141.3	106.7	96.0	135.3	115.86	20.946193
360	105.3	141.3	116.0	108.0	123.3	118.78	14.432844

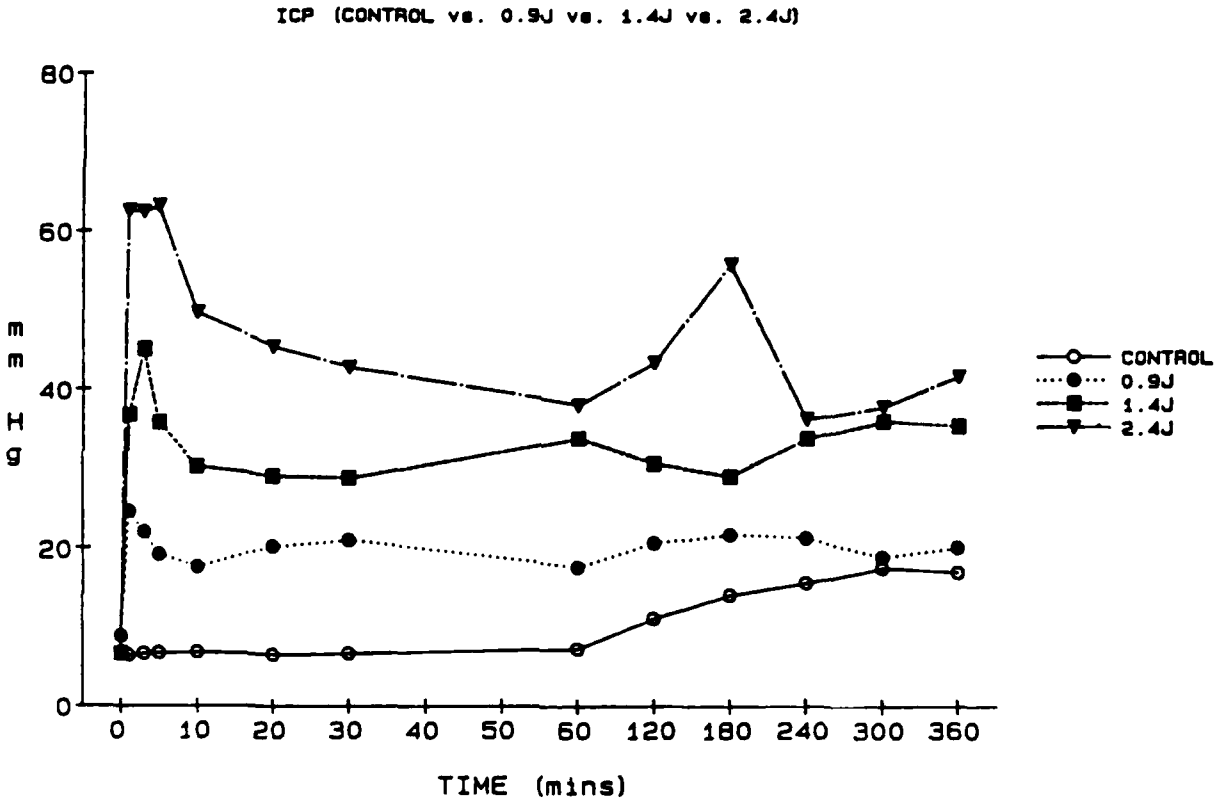
Table 25: Blood Pressure 1.4 Joules

TIME	M225	M228	M234	M237	M243	MEANS	SD
0	96.0	104.0	109.3	116.0	117.3	108.52	8.815157
1	182.0	108.0	141.3	156.0	185.3	154.52	31.794764
3	128.0	98.7	117.3	121.3	148.0	122.66	17.855615
5	106.0	94.7	114.3	114.7	137.3	113.40	15.637775
10	99.3	98.7	108.0	105.3	97.3	101.72	4.657467
20	118.7	128.0	112.0	105.3	56.0	104.00	28.114854
30	118.0	137.3	117.3	109.3	68.0	109.98	25.627466
60	98.0	133.3	130.7	109.3	136.0	121.46	16.846454
120	104.0	116.7	133.3	120.0	134.7	121.74	12.695787
180	103.3	110.7	136.0	124.7	165.3	128.00	24.369858
240	96.7	116.0	145.3	122.0	181.3	132.26	32.438912
300	93.3	114.7	154.7	120.0	168.0	130.14	30.557209
360	94.6	105.3	147.3	107.3	162.7	123.44	29.715114

Table 26: Blood Pressure 2.4 Joules

TIME	M220	M223	M236	M241	M244	MEANS	SD
0	104.0	106.0	142.7	112.0	94.7	111.880	18.314666
1	178.7	124.0	210.7	208.0	136.0	171.480	40.116169
3	134.7	84.0	157.3	113.3	78.7	113.600	33.351012
5	156.0	76.0	156.0	98.7	82.7	113.880	39.324636
10	96.0	66.7	157.3	110.7	85.3	103.200	34.232879
20	61.3	77.3	149.3	113.3	90.7	98.380	34.255394
30	64.0	76.0	149.3	117.3	110.7	103.460	34.118954
60	72.0	65.0	152.7	114.3	176.0	116.000	48.700051
120	65.3	125.3	161.3	129.3	176.0	131.440	42.702436
180	56.7	46.0	233.3	114.7	194.7	129.080	82.039327
240	52.0	48.7	126.7	76.0	197.3	100.140	62.633402
300	68.0	52.0	132.0	80.0	178.7	102.140	52.256081
360	69.3		145.3	82.7	192.0	122.325	57.050409

Figure 49: Intracranial pressures (ICP); controls and cats wounded at 0.9, 1.4, and 2.4 Joules. (means ± S.E. n=5)



Figures 50-53: Intracranial pressure (ICP); controls and cats wounded at 0.9, 1.4, and 2.4 Joules. (means ± S.E. n=5)

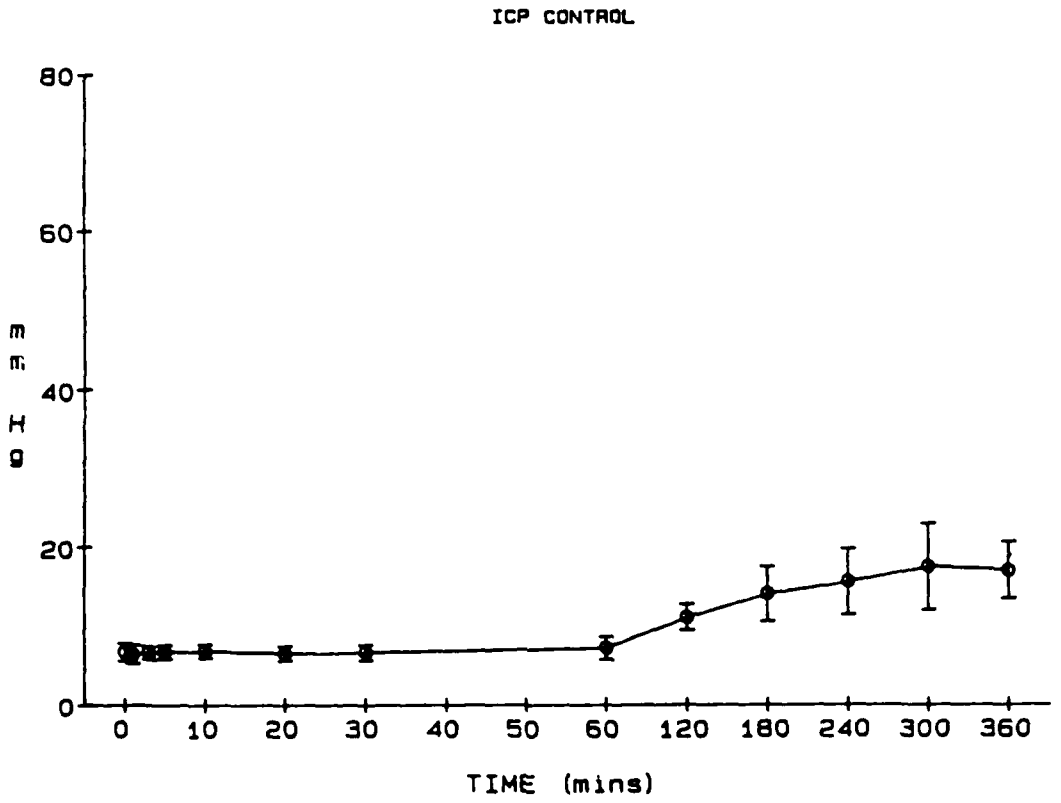


Figure 50

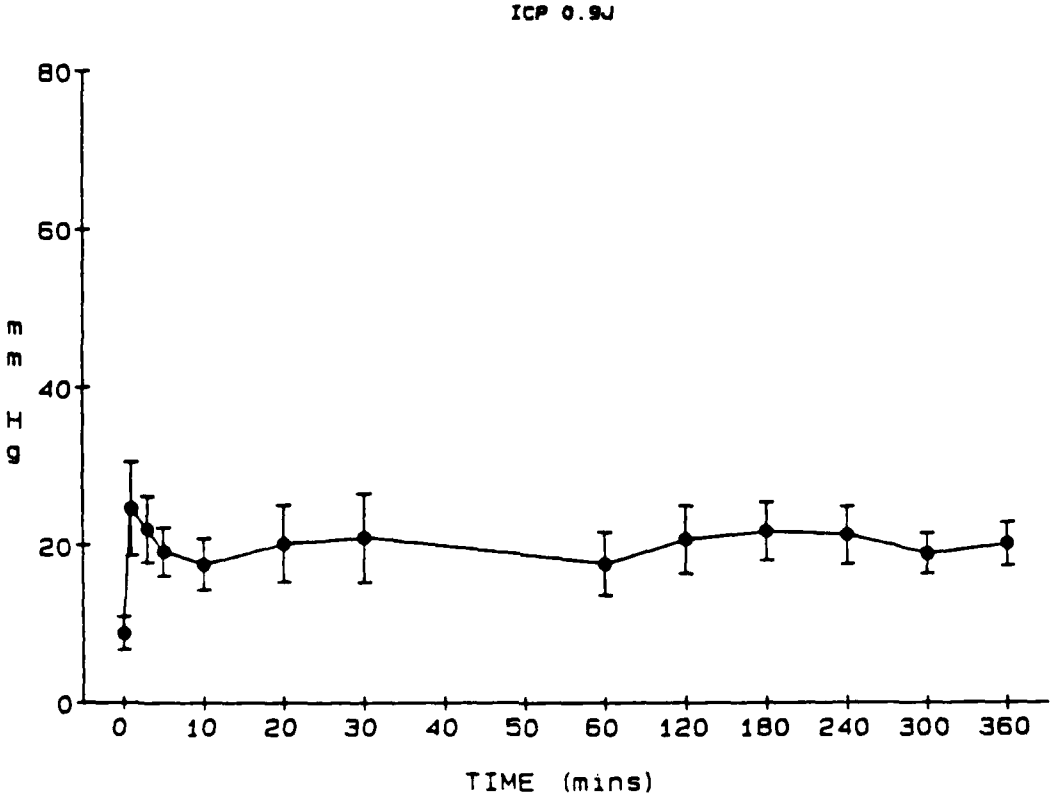


Figure 51

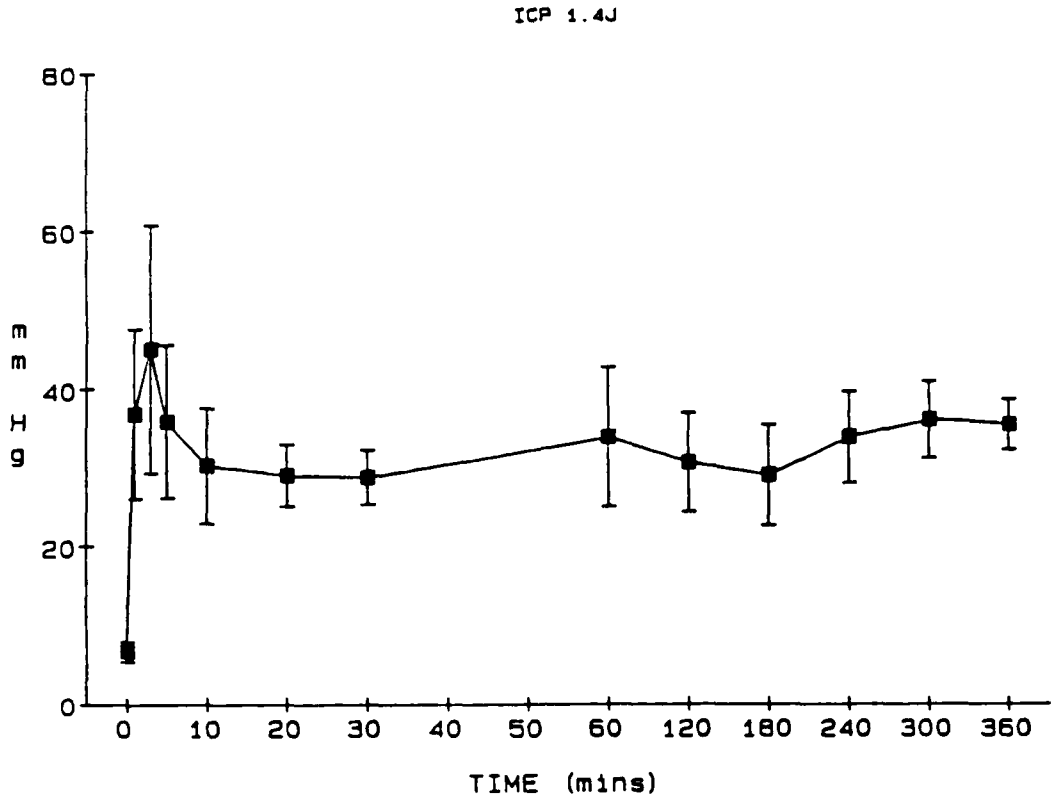


Figure 52

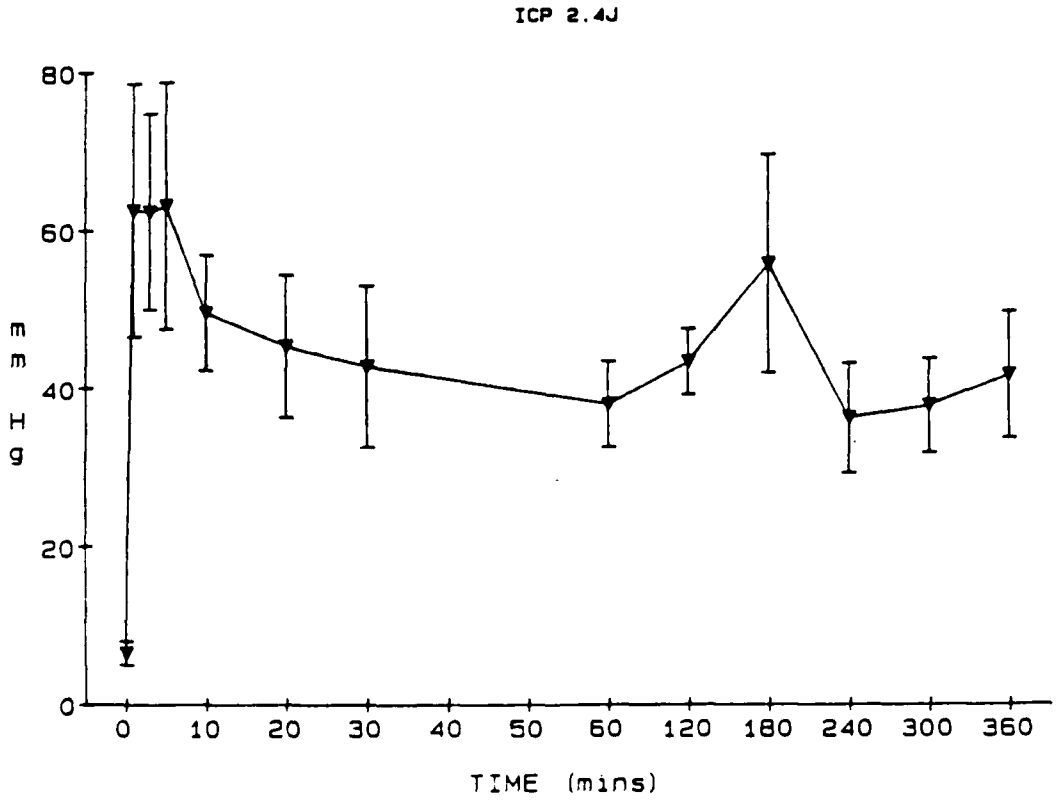


Figure 53

Table 27: Intracranial Pressure Control

TIME	C261	C262	C263	C267	C269	MEANS	SD
0	9.0	8.5	8	4.0	4.0	6.7	2.489980
1	9.5	9.0	6	3.5	4.0	6.4	2.770379
3	9.0	8.0	6	4.0	6.0	6.6	1.949359
5	9.0	8.0	6	3.5	7.0	6.7	2.109502
10	9.0	8.5	6	4.0	6.5	6.8	2.018663
20	8.0	9.0	5	4.0	6.5	6.5	2.061553
30	8.5	9.5	5	4.0	6.0	6.6	2.329163
60	8.0	12.5	5	4.5	6.0	7.2	3.251923
120	14.5	11.0	9	6.0	15.0	11.1	3.781534
180	12.5	11.5	26	4.5	16.0	14.1	7.853343
240	13.0	12.0	29	4.0	20.0	15.6	9.396808
300	12.5	12.0	27	3.0	33.0	17.5	12.206556
360	12.5	15.0	28	7.5	22.0	17.0	8.070006

Table 28: Intracranial Pressure 0.9 Joules

TIME	M219	M227	M231	M233	M239	MEANS	SD
0	7.0	16	8.0	10	3	8.8	4.764452
1	28.0	46	13.0	19	17	24.6	13.164346
3	34.0	30	14.0	14	18	22.0	9.380832
5	26.0	26	17.0	10	17	19.2	6.833740
10	13.0	24	25.0	8	18	17.6	7.231874
20	9.0	22	29.0	9	32	20.2	10.848963
30	8.0	22	38.5	10	26	20.9	12.471969
60	8.0	20	31.0	11	18	17.6	8.961027
120	7.0	29	29.0	15	23	20.6	9.528903
180	9.0	30	27.5	22	20	21.7	8.167007
240	8.0	30	25.0	22	21	21.2	8.167007
300	10.5	26	21.0	17	20	18.9	5.705261
360	10.5	26	25.0	19	20	20.1	6.168468

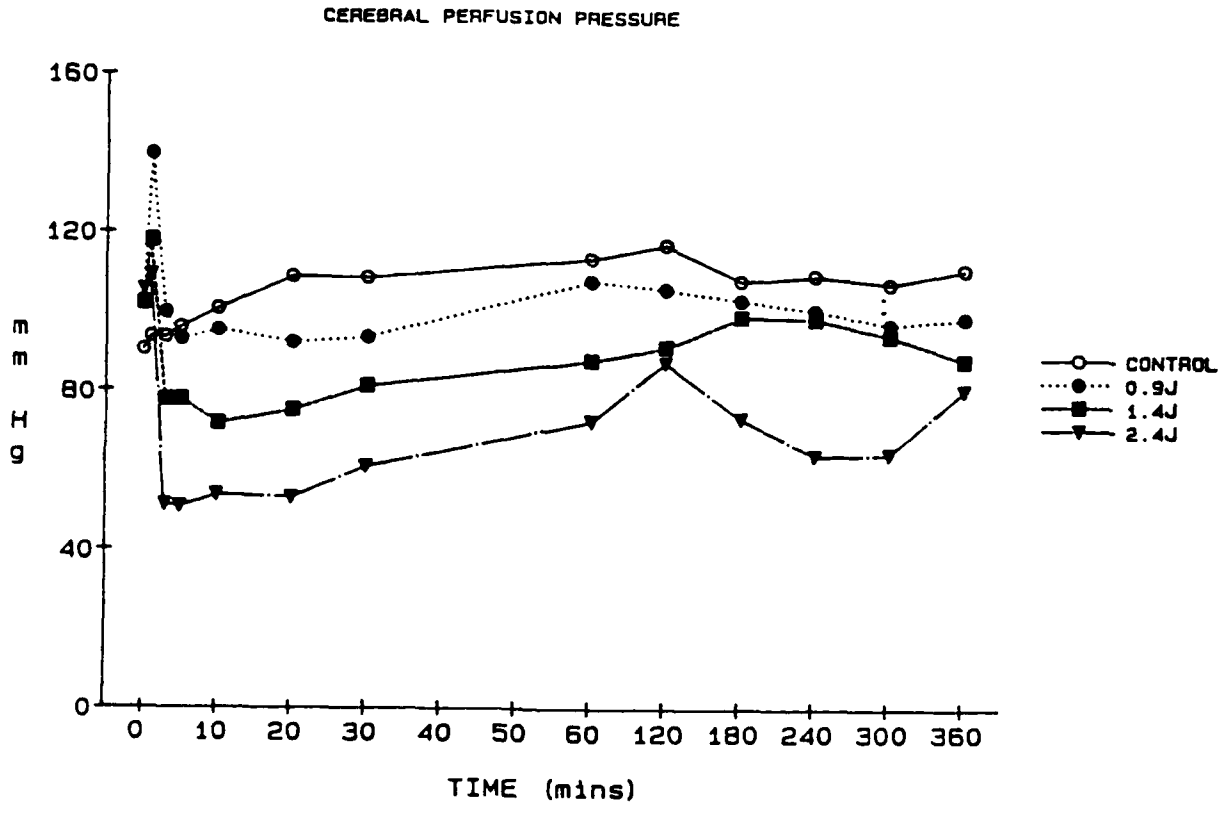
Table 29: Intracranial Pressure 1.4 Joules

TIME	M225	M228	M234	M237	M243	MEANS	SD
0	4	11	5	5	8	6.6	2.880972
1	20	20	36	30	78	36.8	24.024987
3	27	19	30	43	106	45.0	35.178118
5	23	17	29	38	72	35.8	21.672563
10	14	18	31	32	56	30.2	16.437761
20	18	21	33	37	36	29.0	8.860023
30	19	22	33	35	35	28.8	7.694154
60	20	20	40	23	66	33.8	19.829271
120	20	32	35	15	51	30.6	14.081903
180	17	34	27	16	51	29.0	14.370108
240	22	36	26	30	55	33.8	12.930584
300	24	40	28	36	52	36.0	10.954451
360	28	35	31	36	47	35.4	7.231874

Table 30: Intracranial Pressure 2.4 Joules

TIME	M220	M223	M236	M241	M244	MEANS	SD
0	5.3	5	3	7	12	6.46	3.407052
1	126.0	46	52	51	38	62.60	35.871995
3	98.0	72	40	73	29	62.40	27.790286
5	115.0	78	40	57	26	63.20	34.866890
10	60.0	67	48	49	24	49.60	16.349312
20	34.0	77	47	46	23	45.40	20.206435
30	33.0	82	35	41	23	42.80	22.851696
60	48.0	54	29	32	27	38.00	12.186058
120	55.0	46	48	36	32	43.40	9.316652
180	50.0	46	110	34	39	55.80	30.922484
240	58.0	46	19	28	30	36.20	15.594871
300	57.0	46	25	30	31	37.80	13.292855
360	60.0		43	21	43	41.75	15.986974

Figure 54: Cerebral perfusion pressure (CPP); controls and cats wounded at 0.9, 1.4 and 2.4 Joules. (means ± S.E. n=5)



Figures 55-58: Cerebral perfusion pressure (CPP); controls and cats wounded at 0.9, 1.4, and 2.4 Joules (means ± S.E. n=5)

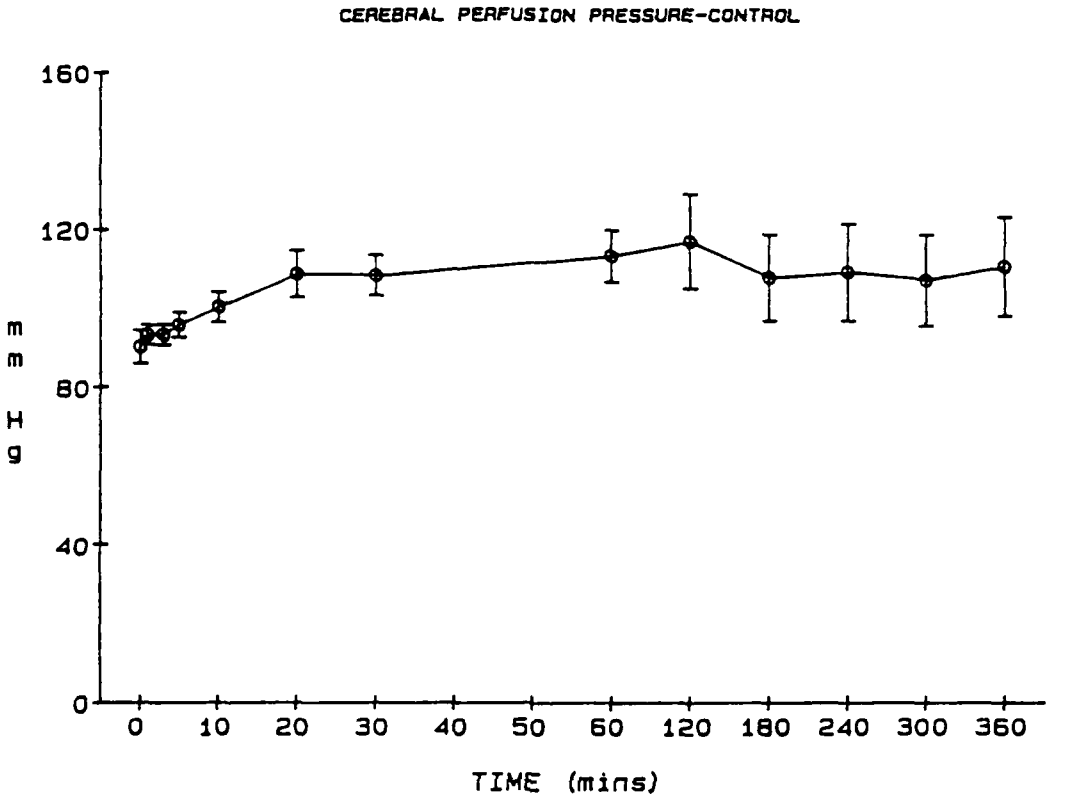


Figure 55

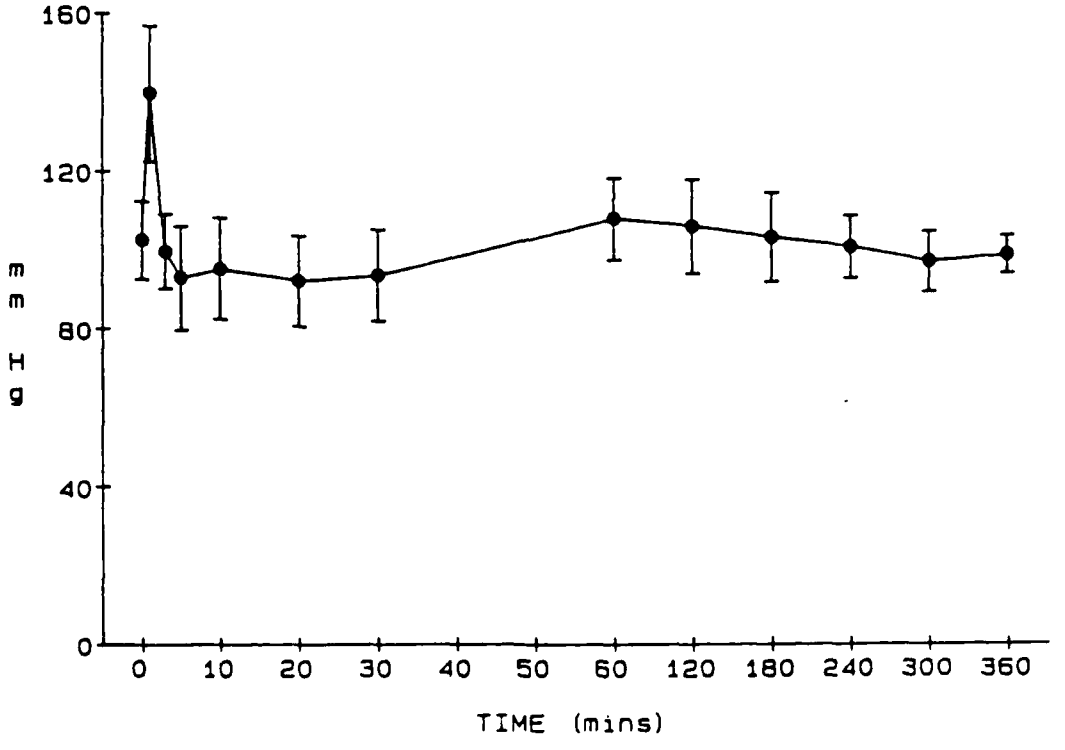


Figure 56

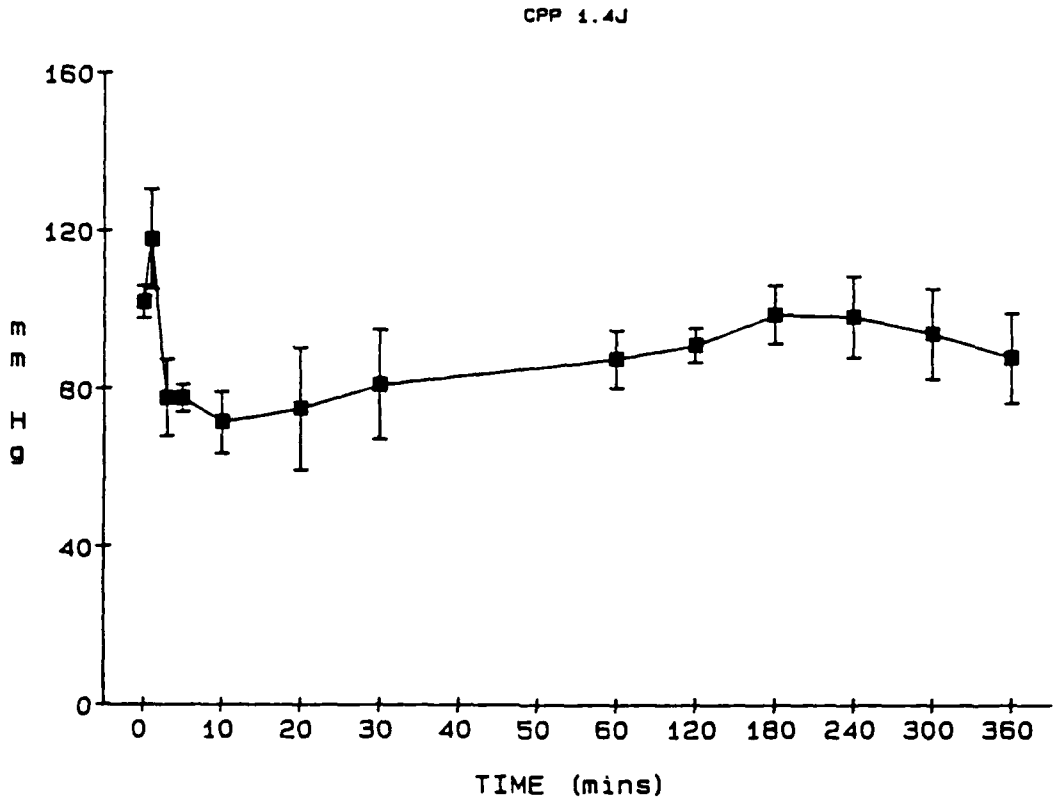


Figure 57

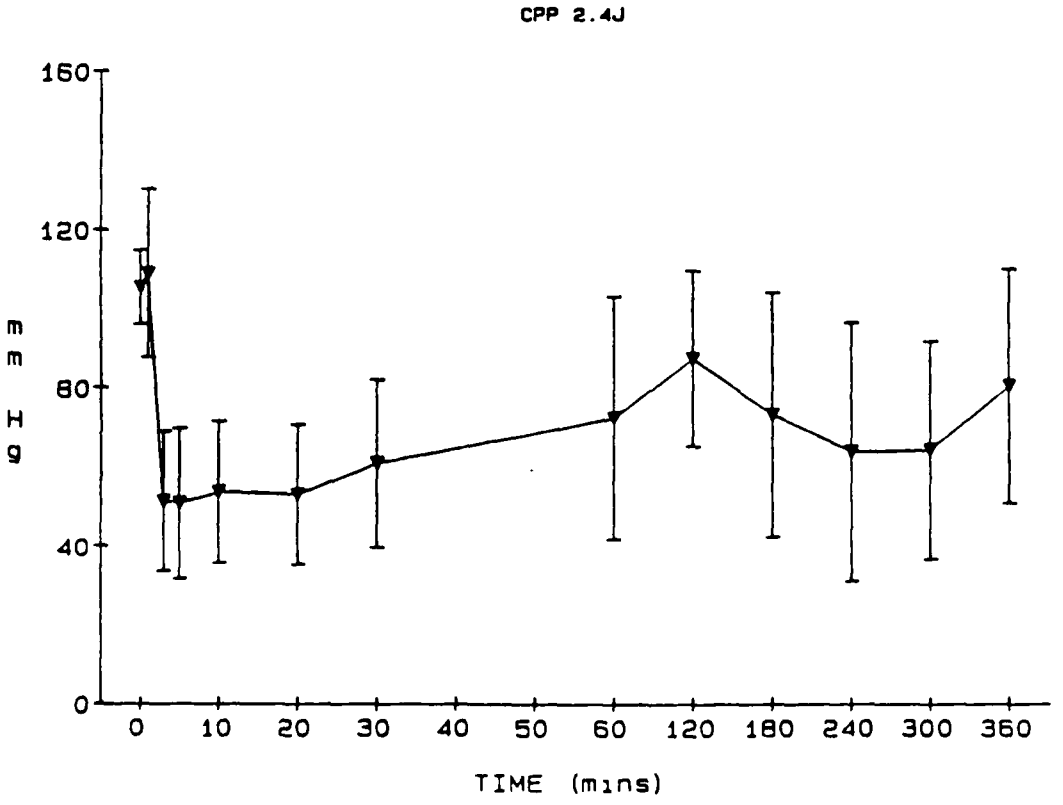


Figure 58

Table 31: Cerebral Perfusion Pressure Control

TIME	C261	C262	C263	C267	C269	MEANS	SD
0	103.0	83.5	84	98.0	83.0	90.3	9.484197
1	97.5	86.0	96	98.5	89.0	93.4	5.561025
3	98.0	90.0	86	101.0	92.0	93.4	6.066300
5	99.0	100.0	87	103.5	90.0	95.9	7.039176
10	114.0	94.5	92	99.0	103.5	100.6	8.684757
20	127.0	104.0	92	106.0	115.5	108.9	13.126309
30	119.5	100.5	93	113.0	117.0	108.6	11.376511
60	100.0	117.5	97	122.5	131.0	113.6	14.643258
120	88.5	91.0	121	147.0	138.0	117.1	26.670208
180	95.5	95.5	87	148.5	114.0	108.1	24.645994
240	92.0	98.0	81	146.0	130.0	109.4	27.400730
300	117.5	98.0	80	147.0	94.0	107.3	25.926820
360	97.5	100.0	80	152.5	125.0	111.0	28.206825

Table 32: Cerebral Perfusion Pressure 0.9 Joules

TIME	M219	M227	M231	M233	M239	MEANS	SD
0	78.3	134.7	90.7	95.3	113.0	102.40	21.930344
1	122.3	163.3	119.0	194.3	99.0	139.58	38.489570
3	86.0	136.7	96.7	87.3	91.3	99.60	21.153959
5	62.0	139.3	91.0	74.0	97.7	92.80	29.544796
10	63.0	140.0	83.0	88.0	102.0	95.20	28.682747
20	71.0	136.7	81.7	83.0	88.0	92.08	25.700914
30	70.0	134.0	75.5	85.3	102.7	93.50	25.828182
60	99.3	140.0	79.7	100.3	119.3	107.72	22.842767
120	97.0	149.7	90.3	82.3	109.7	105.80	26.515844
180	89.0	140.7	80.5	88.0	117.3	103.10	25.263511
240	88.0	123.3	85.7	90.0	116.3	100.66	17.712227
300	89.5	115.3	85.7	79.0	115.3	96.96	17.158904
360	94.8	115.3	91.0	89.0	103.3	98.68	10.785500

Table 33: Cerebral Perfusion Pressure 1.4 Joules

TIME	M225	M228	M234	M237	M243	MEANS	SD
0	92.0	93.0	104.3	111.0	109.3	101.92	8.951927
1	162.0	88.0	105.3	126.0	107.3	117.72	28.175291
3	101.0	79.7	87.3	78.3	42.0	77.66	21.874026
5	83.0	77.7	85.3	76.7	65.3	77.60	7.754998
10	85.3	80.7	77.0	73.3	41.3	71.52	17.468600
20	100.7	107.0	79.0	68.3	20.0	75.00	34.533969
30	99.0	115.3	84.3	74.3	33.0	81.18	31.064884
60	78.0	113.3	90.7	86.3	70.0	87.66	16.383620
120	84.0	84.7	98.3	105.0	83.7	91.14	9.889034
180	86.3	76.7	109.0	108.7	114.3	99.00	16.483022
240	74.7	80.0	119.3	92.0	126.3	98.46	23.218592
300	69.3	74.7	126.7	84.0	116.0	94.14	25.669885
360	66.6	70.3	116.3	71.3	115.7	88.04	25.584722

Table 34: Cerebral Perfusion Pressure 2.4 Joules

TIME	M220	M223	M236	M241	M244	MEANS	SD
0	98.7	101.0	139.7	105.0	82.7	105.420	20.953448
1	52.7	78.0	158.7	157.0	98.0	108.880	47.501863
3	36.7	12.0	117.3	40.3	49.7	51.200	39.487846
5	41.0	-2.0	116.0	41.7	56.7	50.680	42.580712
10	36.0	-0.3	109.3	61.7	61.3	53.600	40.132157
20	27.3	0.3	102.3	67.3	67.7	52.980	39.651129
30	31.0	-5.0	114.3	76.3	87.7	60.860	47.549374
60	24.0	-17.0	123.7	82.7	149.0	72.480	68.811750
120	10.3	76.3	113.3	93.3	144.0	87.440	49.941946
180	6.7	0.0	123.3	80.7	155.7	73.280	69.197124
240	-6.0	2.7	107.7	48.0	167.3	63.940	73.304591
300	11.0	6.0	107.0	50.0	147.7	64.340	61.690988
360	9.3		102.3	61.7	149.0	80.575	59.414778

Figures 59-62: Heart rate; controls and cats wounded at 0.9, 1.4 and 2.4 Joules. (means ± S.E. n=5)

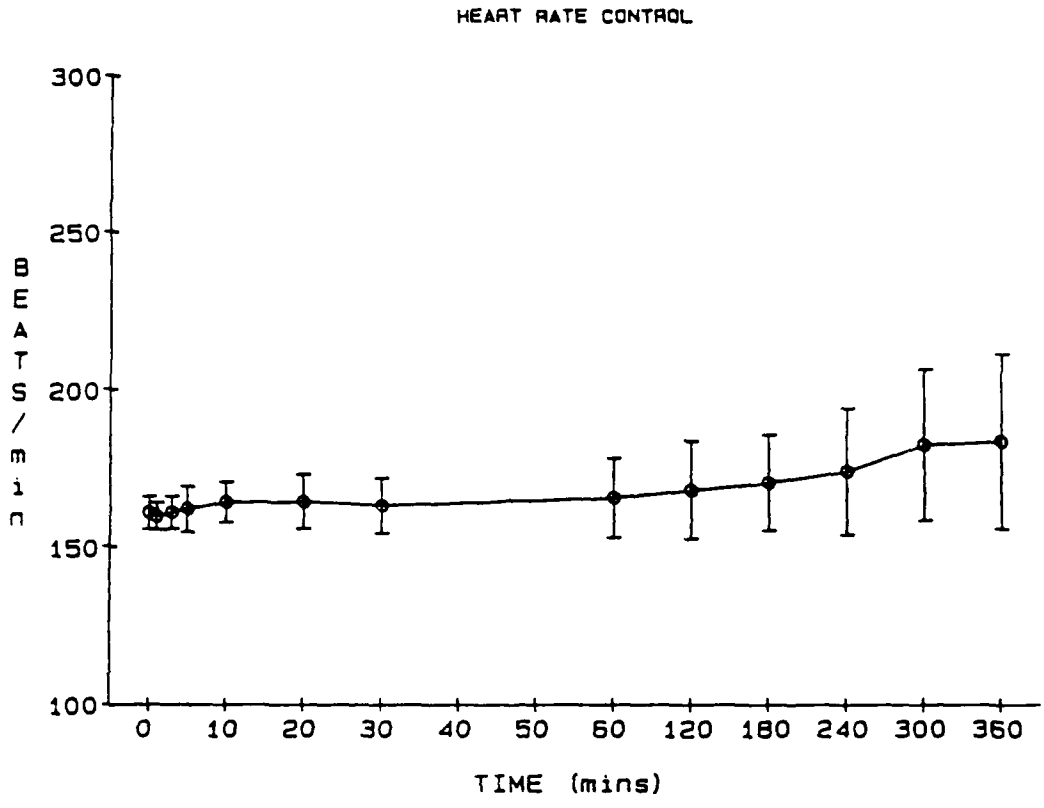


Figure 59

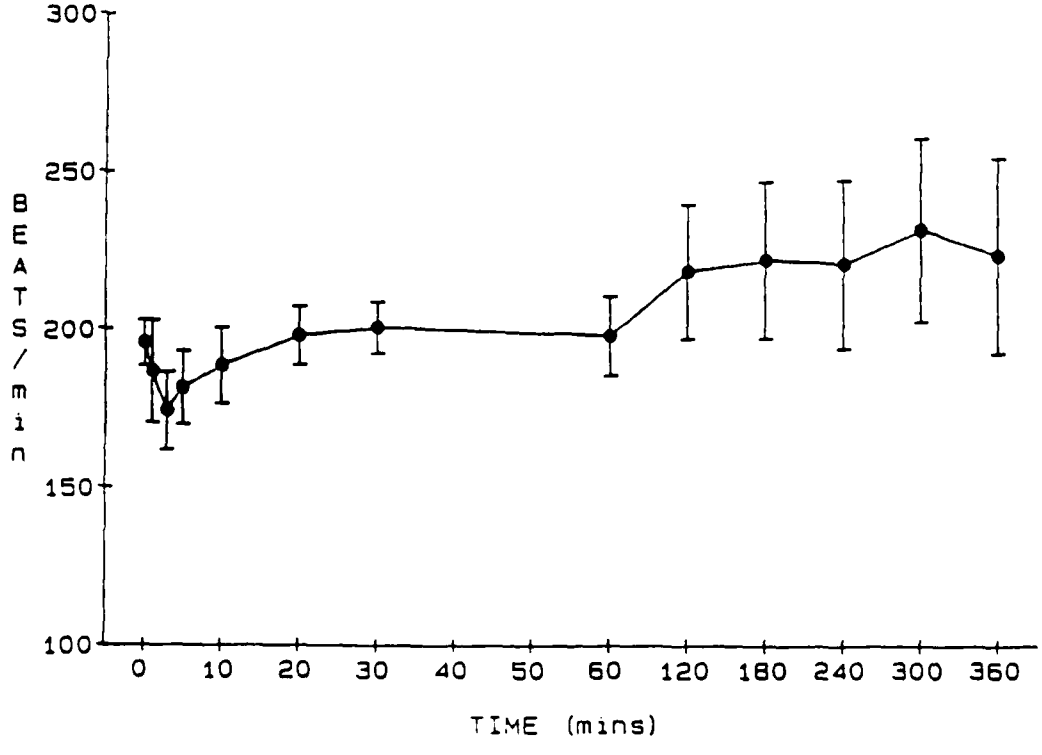


Figure 60

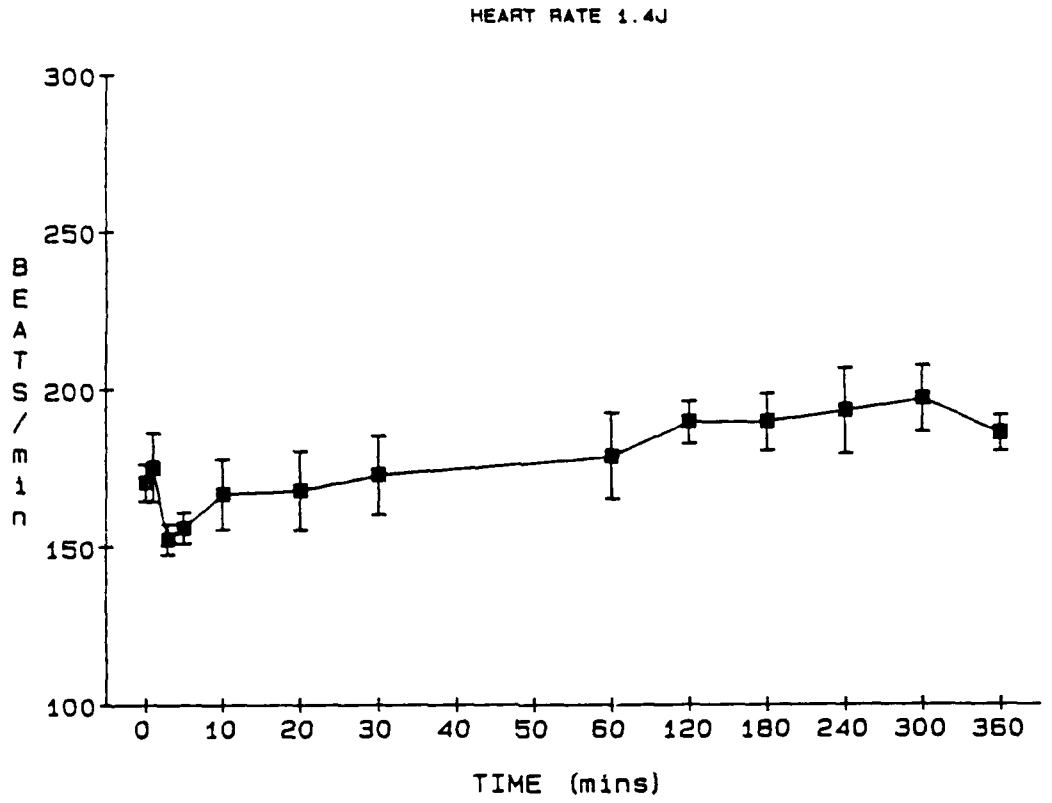


Figure 61

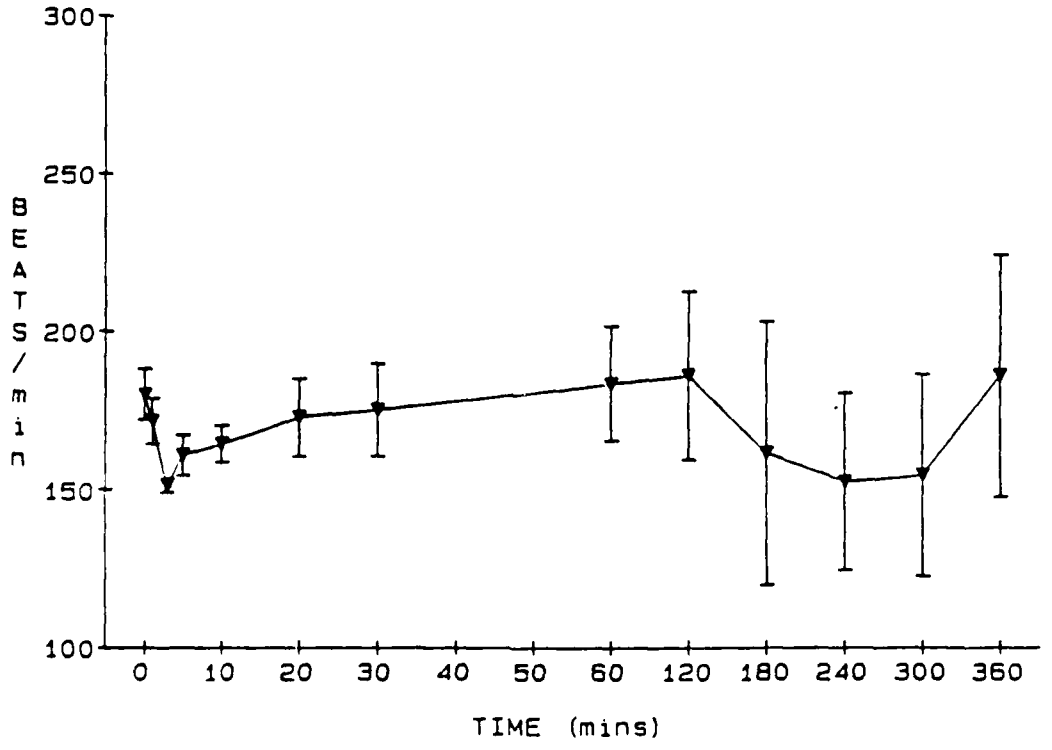


Figure 62

Table 35: Heart Rate Control

TIME	C261	C262	C263	C267	C269	MEANS	SD
0	156	168	144	174	162	160.8	11.541230
1	156	168	144	168	162	159.6	10.039920
3	156	174	144	168	162	160.8	11.541230
5	156	180	138	174	162	162.0	16.431677
10	156	180	144	174	168	164.4	14.449913
20	156	180	138	186	162	164.4	19.256168
30	156	180	138	186	156	163.2	19.626513
60	138	186	144	204	156	165.6	28.333725
120	120	156	174	216	174	168.0	34.727511
180	120	174	168	216	174	170.4	34.099853
240	108	180	168	234	180	174.0	44.899889
300	114	162	162	234	240	182.4	53.598507
360	102	156	168	252	240	183.6	62.296067

Table 36: Heart Rate 0.9 Joules

TIME	M219	M227	M231	M233	M239	MEANS	SD
0	222	192	180	186	198	195.6	16.211107
1	210	122	198	198	204	186.4	36.342812
3	174	156	180	144	216	174.0	27.495454
5	174	180	180	150	222	181.2	25.946098
10	180	180	186	162	234	188.4	27.033313
20	210	180	192	180	228	198.0	20.784610
30	210	186	192	186	228	200.4	18.297541
60	246	174	186	198	186	198.0	28.142495
120	264	174	186	192	276	218.4	47.736778
180	276	168	186	192	288	222.0	55.641711
240	276	162	186	186	294	220.8	59.759518
300	300	156	198	204	300	231.6	65.121425
360	300	150	234	210		223.5	62.040309

Table 37: Heart Rate 1.4 Joules

TIME	M225	M228	M234	M237	M243	MEANS	SD
0	162	192	162	162	174	170.4	13.145341
1	216	150	168	174	168	175.2	24.519380
3	138	156	144	162	162	152.4	10.899541
5	144	168	144	162	162	156.0	11.224972
10	162	210	144	156	162	166.8	25.242821
20	168	216	150	150	156	168.0	27.820855
30	168	222	162	156	156	172.8	27.949955
60	162	228	186	150	168	178.8	30.417100
120	180	216	186	186	180	189.6	15.059880
180	180	216	162	198	192	189.6	20.169284
240	186	240	156	198	186	193.2	30.417100
300	180	234	174	198	198	196.8	23.392306
360	186	168	198	180	198	186.0	12.727922

Table 38: Heart Rate 2.4 Joules

TIME	M220	M223	M236	M241	M244	MEANS	SD
0	150	186	186	198	180	180.0	18.000000
1	180	162	150	192	174	171.6	16.211107
3	156	150	156	150	144	151.2	5.019960
5	180	150	162	168	144	160.8	14.324804
10	144	180	168	168	162	164.4	13.145341
20	126	186	174	198	180	172.8	27.626075
30	120	186	174	204	192	175.2	32.698624
60	120	168	204	222	204	183.6	40.605418
120	108	144	210	258	210	186.0	59.548300
180	88	96		258	204	161.5	83.288655
240	84	90	168	222	198	152.4	62.727984
300	82	78	180	240	192	154.4	71.545790
360	84		198	270	192	186.0	76.681158

Figures 63-66: Respiratory rate; controls and cats wounded at 0.9, 1.4 and 2.4 Joules. (means ± S.E. n=5)

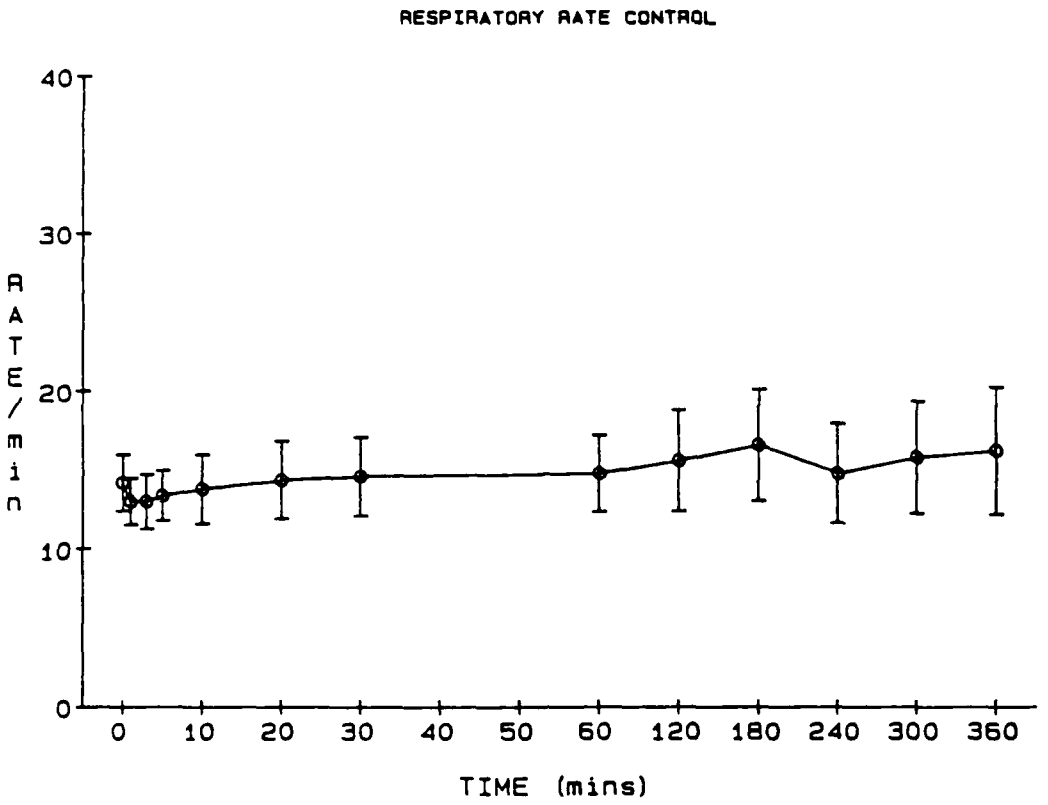


Figure 63

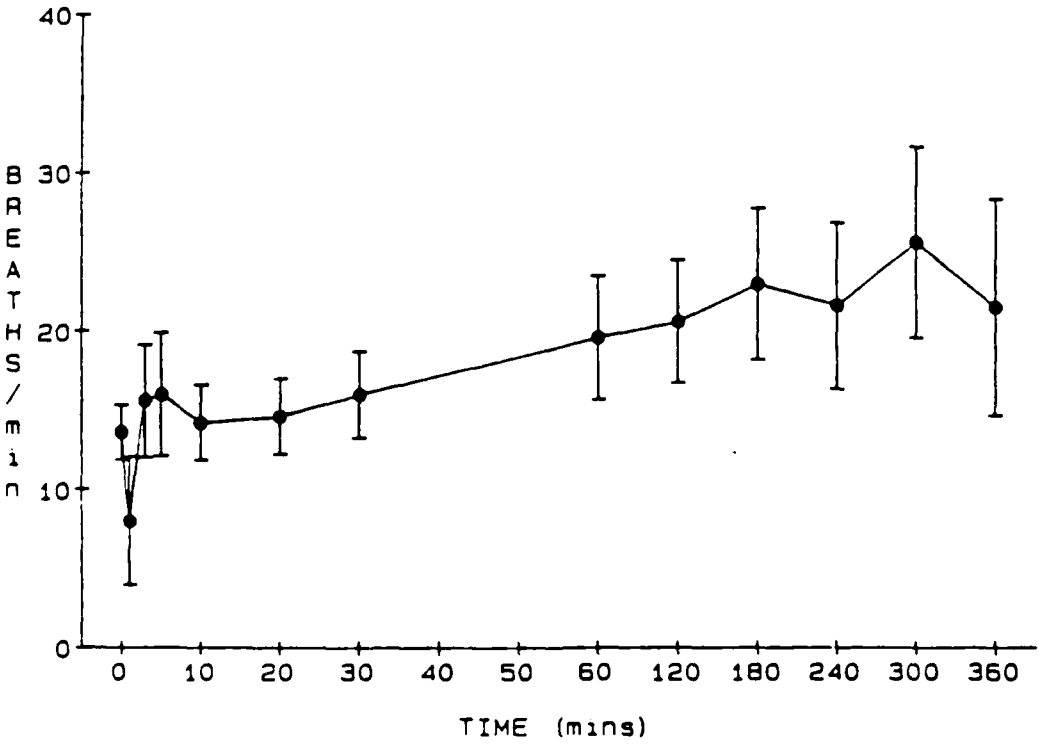


Figure 64

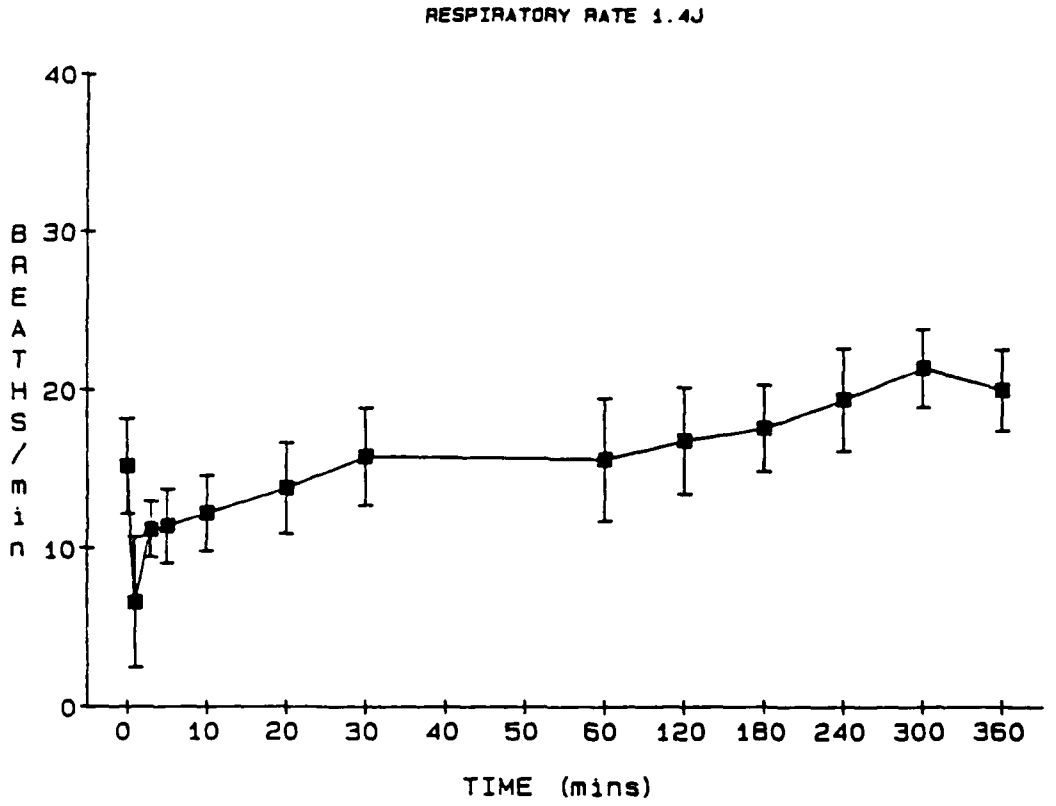


Figure 65

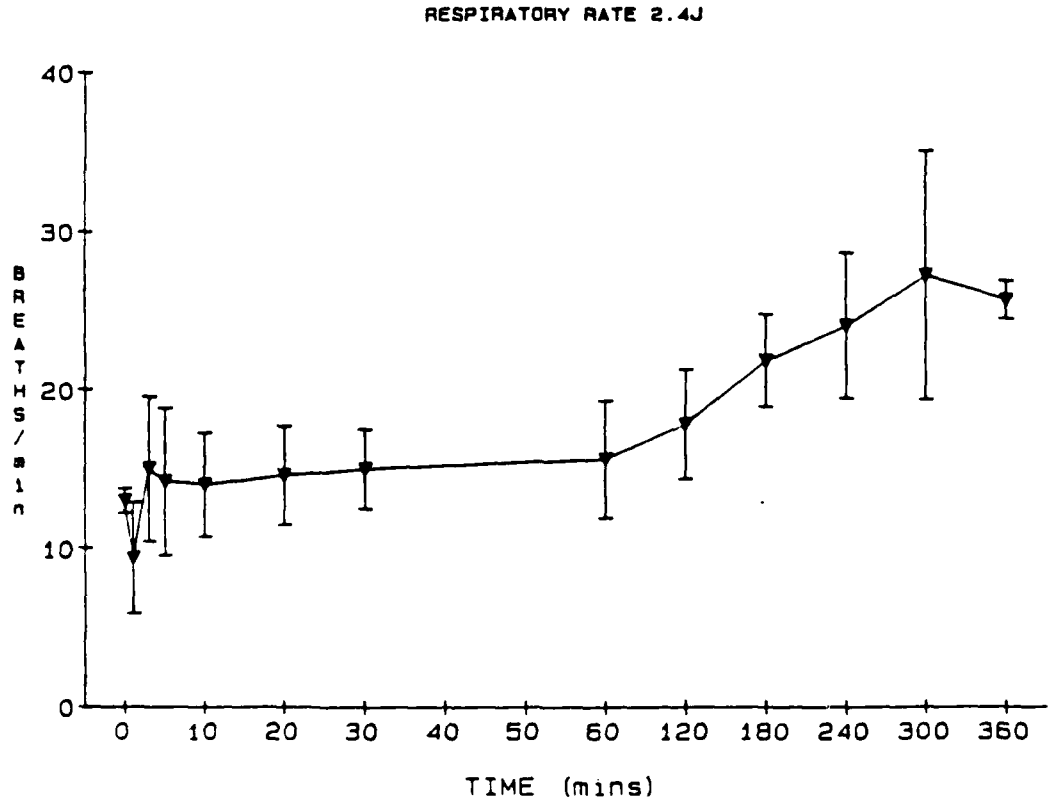


Figure 66

Table 39: Respiratory Rate Control

TIME	C261	C262	C263	C267	C269	MEANS	SD
0	10	19	12	12	18	14.2	4.024922
1	10	17	10	12	16	13.0	3.316625
3	9	16	10	12	18	13.0	3.872983
5	9	16	12	12	18	13.4	3.577709
10	9	20	10	12	18	13.8	4.919350
20	9	22	10	13	18	14.4	5.504544
30	8	22	11	14	18	14.6	5.549775
60	8	20	10	18	18	14.8	5.403702
120	8	14	10	24	22	15.6	7.127412
180	8	14	12	28	21	16.6	7.924645
240	7	16	8	22	21	14.8	7.049823
300	7	14	10	24	24	15.8	7.886698
360	6	14	10	24	27	16.2	9.011104

Table 40: Respiratory Rate 0.9 Joules

TIME	M219	M227	M231	M233	M239	MEANS	SD
0	18	14	8	12	16	13.6	3.847077
1	0	8	10	0	22	8.0	9.055385
3	8	17	8	27	18	15.6	7.956130
5	8	19	7	28	18	16.0	8.689074
10	12	19	6	18	16	14.2	5.310367
20	15	20	6	18	14	14.6	5.366563
30	19	22	6	18	15	16.0	6.123724
60	20	30	6	19	23	19.6	8.734987
120	26	26	6	19	26	20.6	8.706320
180	27	34	6	20	28	23.0	10.723805
240	29	32	6	12	29	21.6	11.760102
300	30	32	8	16	42	25.6	13.520355
360	30	36	7	13		21.5	13.723459

Table 41: Respiratory Rate 1.4 Joules

TIME	M225	M228	M234	M237	M243	MEANS	SD
0	20	24	8	14	10	15.2	6.723095
1	0	19	0	0	14	6.6	9.208692
3	17	12	8	12	7	11.2	3.962323
5	16	18	7	9	7	11.4	5.224940
10	17	19	8	9	8	12.2	5.357238
20	22	19	8	8	12	13.8	6.418723
30	24	22	10	9	14	15.8	6.870226
60	26	24	10	10	8	15.6	8.648699
120	26	24	12	12	10	16.8	7.563068
180	26	22	14	14	12	17.6	6.066300
240	30	24	15	14	14	19.4	7.266361
300	28	25	18	14	22	21.4	5.549775
360		22	18	14	26	20.0	5.163978

Table 42: Respiratory Rate 2.4 Joules

TIME	M220	M223	M236	M241	M244	MEANS	SD
0	12	12	13	12	16	13.000000	1.732051
1	12	6	8	0	21	9.400000	7.797435
3	9	6	12	32	16	15.000000	10.198039
5	9	6	10	32	14	14.200000	10.353743
10	26	9	10	9	16	14.000000	7.314369
20	26	9	12	10	16	14.600000	6.913754
30	21	9	12	12	21	15.000000	5.612486
60	24	5	13	12	24	15.600000	8.264381
120	10	13	14	28	24	17.800000	7.758866
180	20	15	18	32	24	21.800000	6.572671
240	26	12	22	40	20	24.000000	10.295630
300	26	8	22	56	24	27.200000	17.584084
360	24		28		25	25.666667	2.081666

Figures 67-70: Arterial blood pCO_2; controls and cats wounded at 0.9, 1.4 and 2.4 Joules. (means ± S.E. n=5)

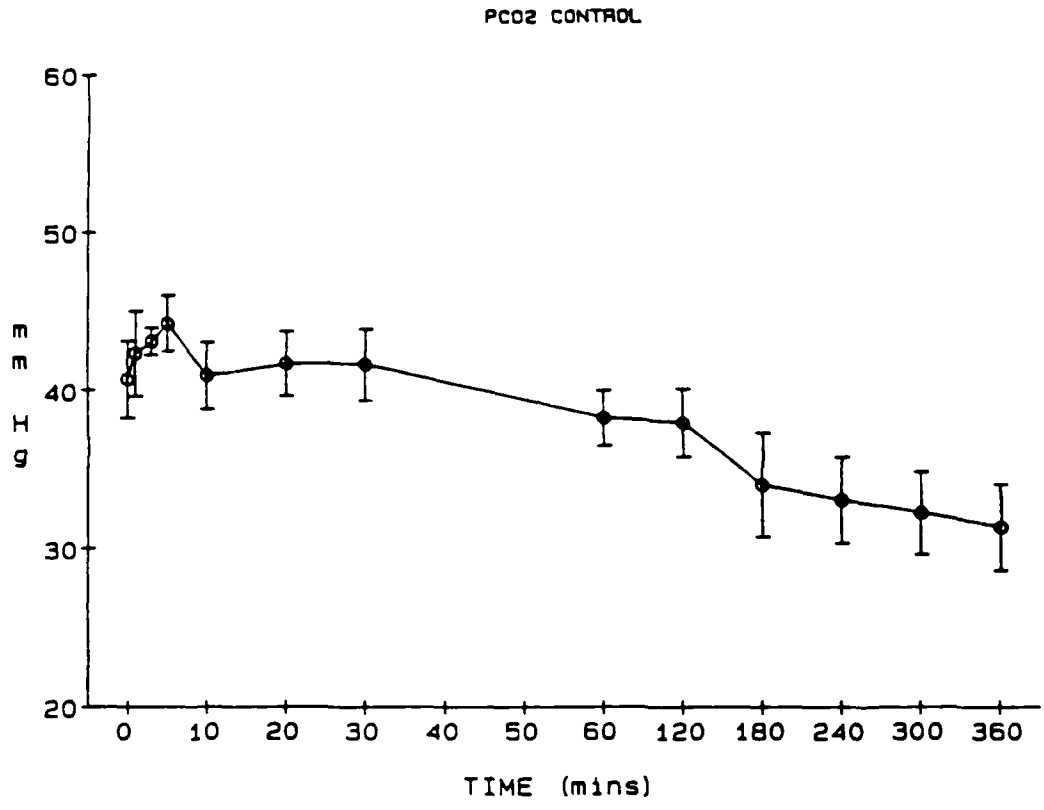


Figure 67

PCO2

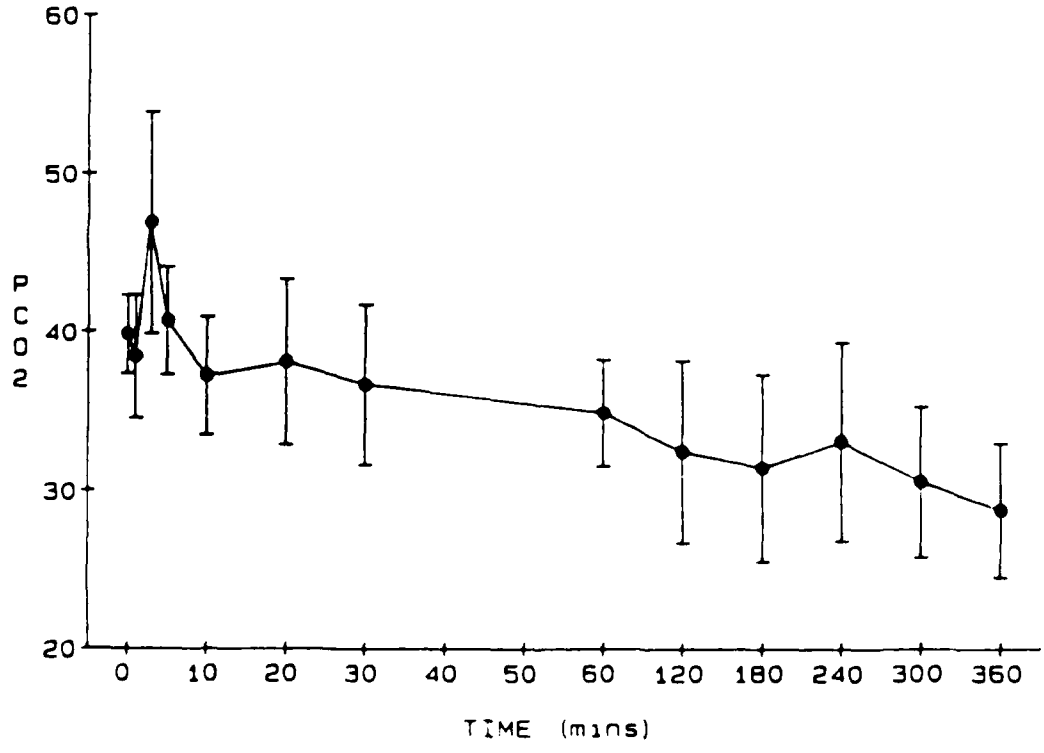


Figure 68

PCO2

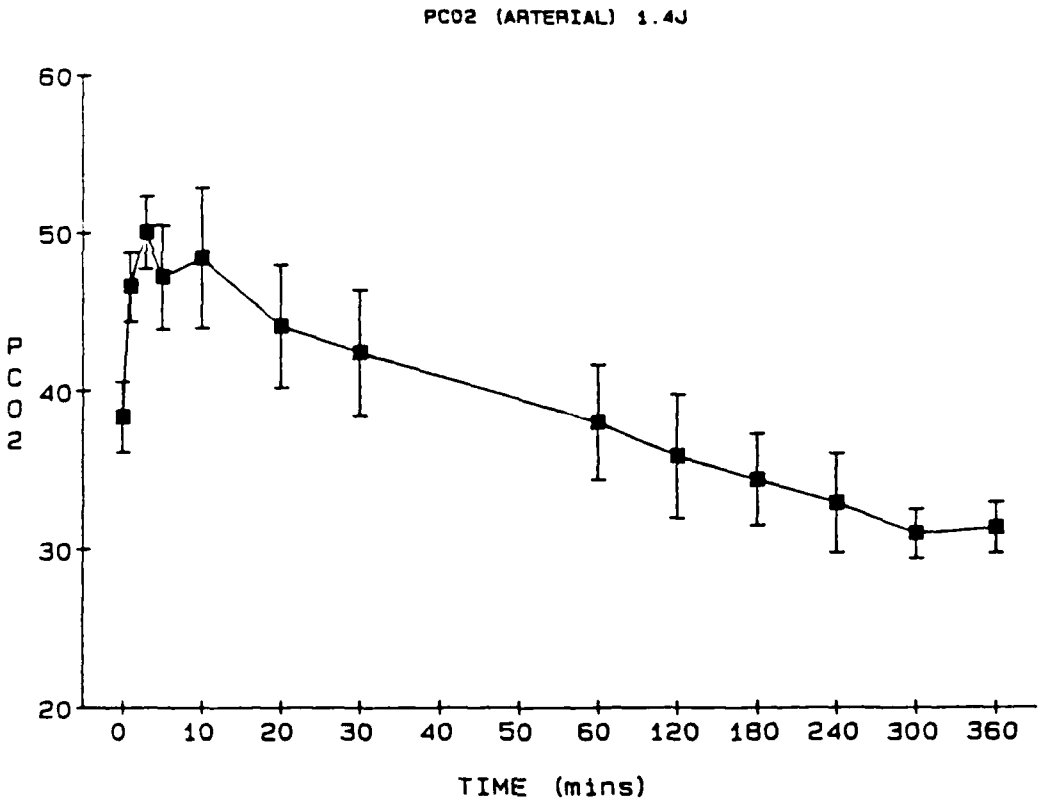


Figure 69

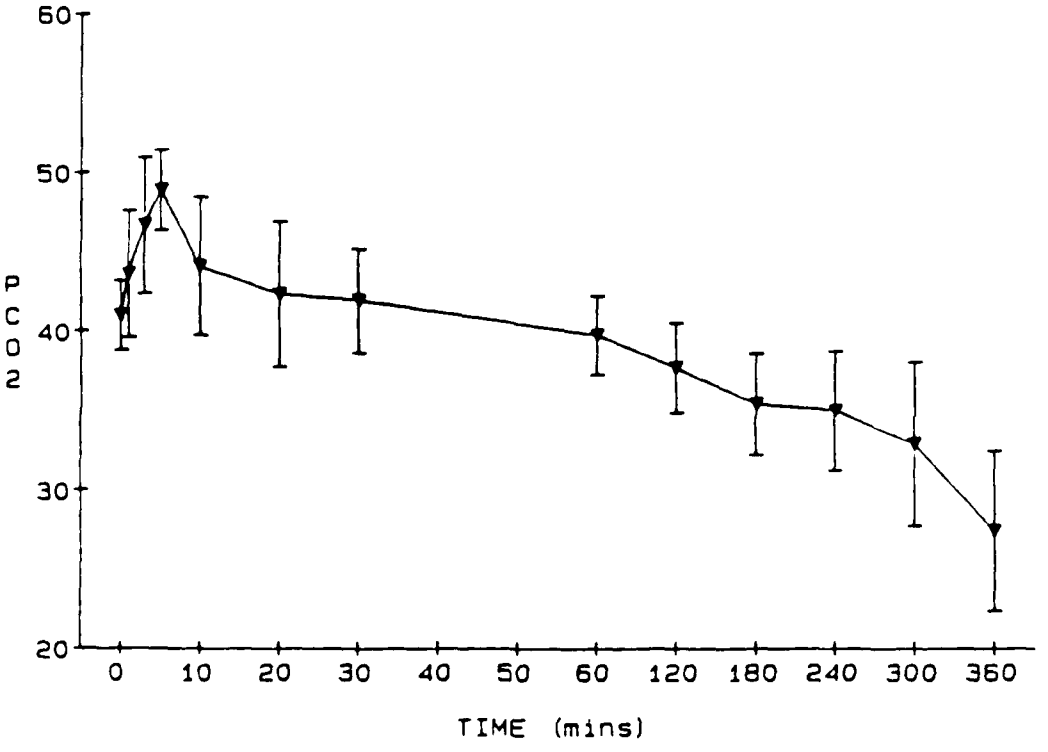


Figure 70

Table 43: pCO_2 Control

TIME	C261	C262	C263	C267	C269	MEANS	SD
0	50.0	37.2	39.7	40.3	36.3	40.70	5.460311
1	52.9	39.9	40.9	40.6	37.4	42.34	6.061600
3	43.9	44.9	44.0	42.8	39.9	43.10	1.937782
5	49.9	41.4	46.9	42.0	41.1	44.26	3.938655
10	35.6	38.8	48.3	42.2	39.9	40.96	4.741624
20	38.7	40.0	49.6	41.8	38.6	41.74	4.580175
30	39.9	38.2	50.6	40.6	38.9	41.64	5.092445
60	39.6	34.0	41.7	34.2	41.9	38.28	3.921352
120	39.0	38.2	42.7	30.0	40.0	37.98	4.773049
180	23.6	38.3	38.4	29.1	40.9	34.06	7.375839
240	27.1	33.3	37.0	27.1	41.0	33.10	6.116780
300	28.2	38.1	39.1	27.0	28.8	32.24	5.852606
360		38.4	32.9	27.1	27.0	31.35	5.449465

Table 44: pCO_2 0.9 Joules

TIME	M219	M227	M231	M233	M239	MEANS	SD
0	37.8	31.8	46.8	42.0	40.8	39.84	5.541480
1	26.4	35.7	50.4	39.7	39.9	38.42	8.649104
3	72.3	32.9	50.5	36.8	41.8	46.86	15.669493
5	42.6	33.1	51.8	33.9	42.0	40.68	7.624107
10	30.1	30.5	50.0	34.7	40.8	37.22	8.341882
20	23.5	33.2	53.9	34.7	45.1	38.08	11.697949
30	24.2	30.6	53.7	33.6	41.2	36.66	11.317155
60	32.5	27.3	47.5	34.8	32.4	34.90	7.558770
120	21.1	24.6	53.8	33.9	28.8	32.44	12.861687
180	18.0	24.6	52.3	35.0	27.2	31.42	13.164422
240	22.8	23.9	56.6	35.4	26.8	33.10	14.035313
300	23.4	25.0	49.0	30.0	25.3	30.54	10.608864
360	19.6	24.5	43.7	31.8	24.1	28.74	9.436790

Table 45: pCO_2 1.4 Joules

TIME	M225	M228	M234	M237	M243	MEANS	SD
0	29.9	40.7	38.0	40.9	42.3	38.36	4.978755
1	41.4	41.9	46.9	50.9	51.9	46.60	4.893874
3	46.7	44.9	47.4	55.5	55.6	50.02	5.130010
5	44.3	39.9	44.5	47.9	59.4	47.20	7.387828
10	40.6	38.3	47.9	52.5	62.9	48.44	9.876133
20	33.7	37.9	43.5	50.7	54.7	44.10	8.701724
30	32.5	35.0	41.7	50.6	52.3	42.42	8.923396
60	29.9	30.3	39.4	41.1	49.4	38.02	8.161311
120	27.2	32.1	34.3	35.2	50.5	35.86	8.751171
180	27.1	34.4	32.6	33.0	44.9	34.40	6.494998
240	26.4	28.6	35.6	30.1	43.9	32.92	7.015483
300	26.1	28.7	32.7	32.8	34.5	30.96	3.452246
360	25.3	32.4	32.0	32.2	34.9	31.36	3.586502

Table 46: pCO_2 2.4 Joules

TIME	M220	M223	M236	M241	M244	MEANS	SD
0	32.7	44.0	43.5	44.6	40.1	40.98	4.947424
1	31.5	36.6	48.7	50.3	50.9	43.60	8.938680
3	39.0	52.3	56.9	34.1	50.9	46.64	9.631615
5	41.9	57.7	48.5	49.2	47.2	48.90	5.691661
10	27.1	50.4	49.6	48.7	44.7	44.10	9.752692
20	24.4	46.4	46.9	49.9	44.0	42.32	10.235087
30	29.5	47.8	44.5	46.5	41.3	41.92	7.362880
60	37.7	48.9	40.0	38.1	34.0	39.74	5.562643
120	44.8	42.7	38.2	29.7	32.9	37.66	6.377539
180	44.4	37.0	38.7	25.9	30.9	35.38	7.158003
240	45.2	40.0	32.1	23.0	34.5	34.96	8.391841
300	32.4	51.0	34.1	19.7	27.2	32.88	11.576139
360	30.5		39.1	15.0	25.0	27.40	10.099835

Figures 71-74: Arterial blood pH; controls and cats wounded at 0.9, 1.4 and 2.4 Joules. (means ± S.E. n=5)

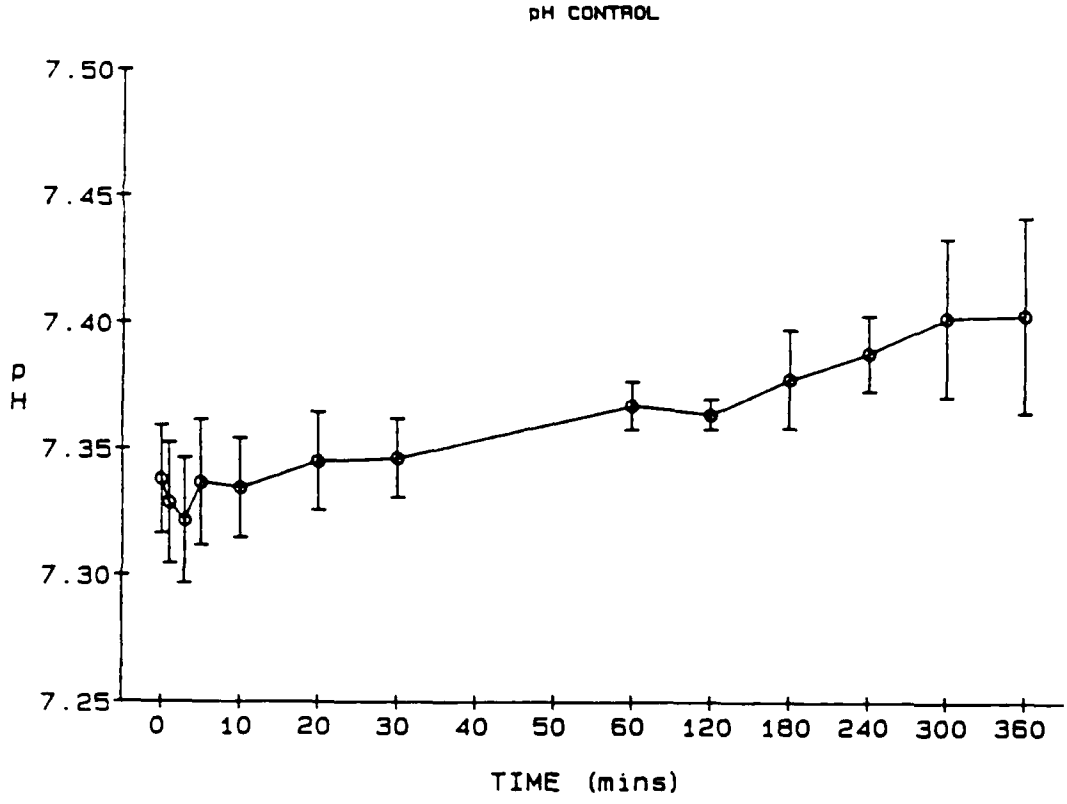


Figure 71

pH

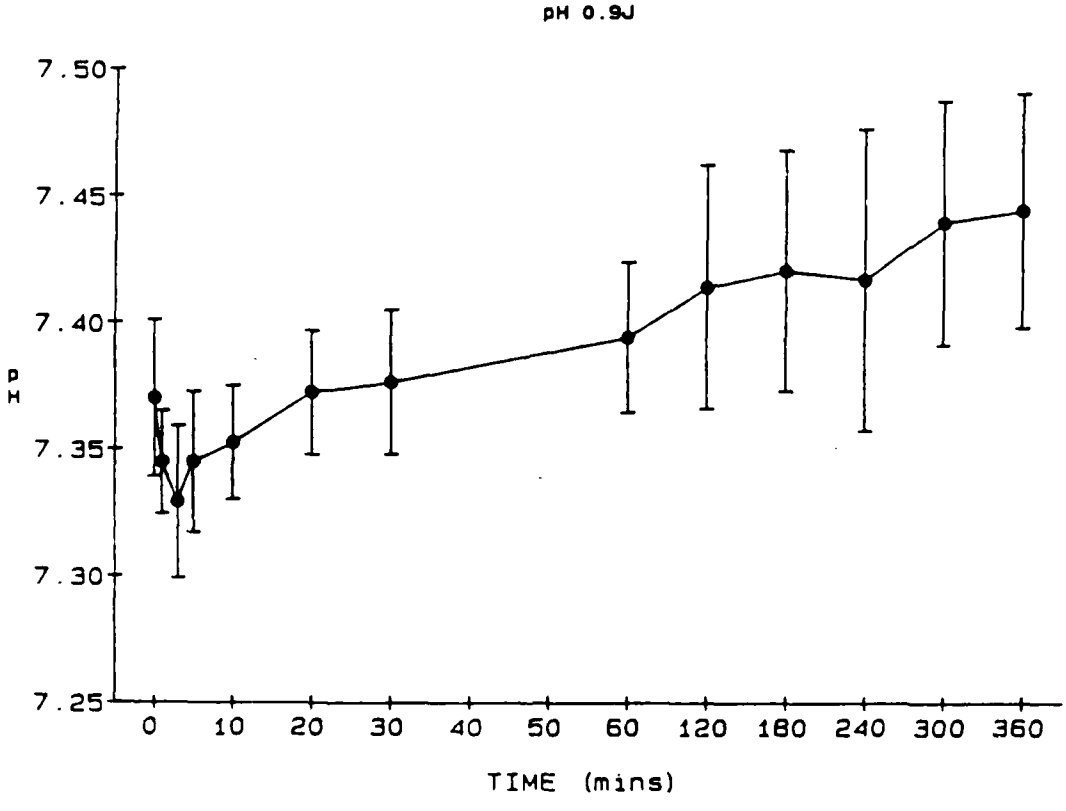


Figure 72

pH

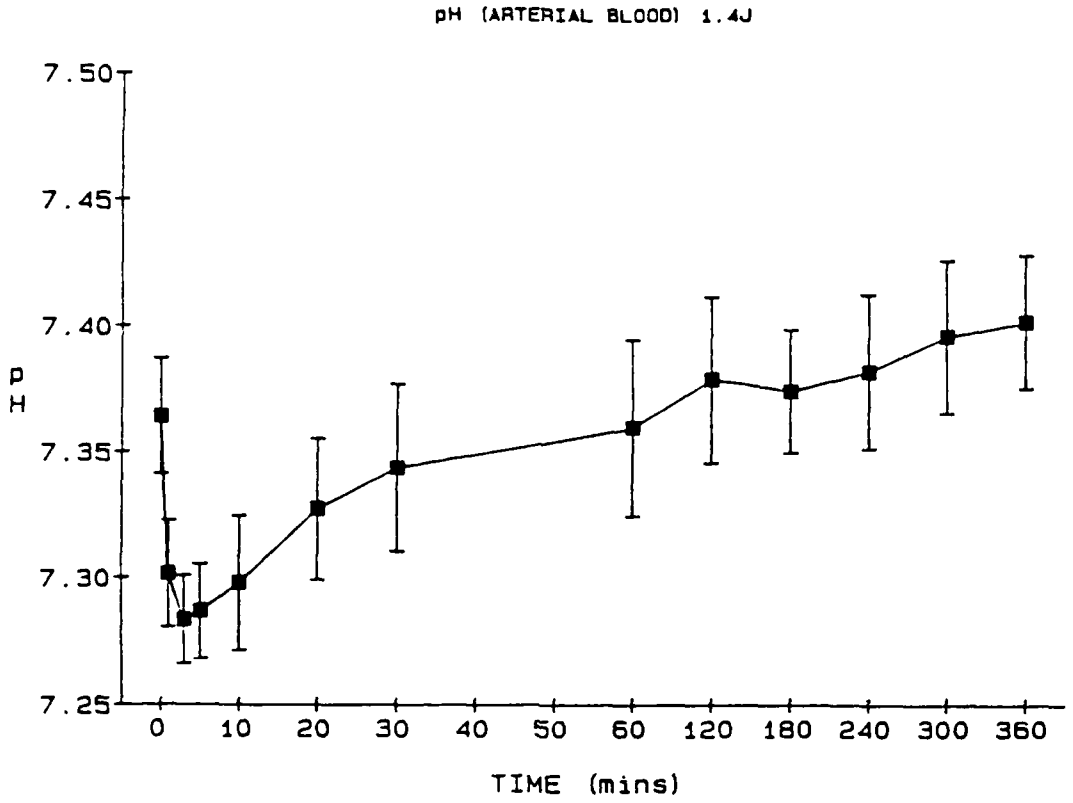


Figure 73

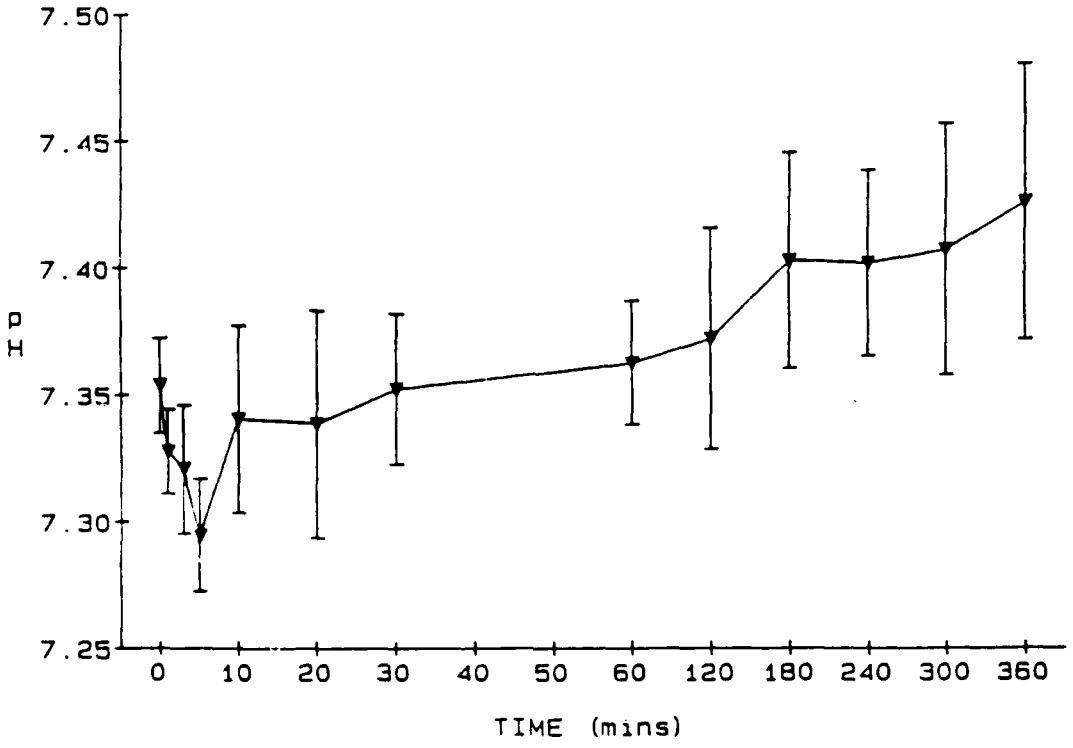


Figure 74

Table 47: pH Control

TIME	C261	C262	C263	C267	C269	MEANS	SD
0	7.390	7.343	7.357	7.260	7.339	7.33780	0.047893
1	7.388	7.326	7.349	7.242	7.337	7.32840	0.053668
3	7.396	7.304	7.344	7.244	7.319	7.32140	0.055622
5	7.408	7.331	7.334	7.253	7.357	7.33660	0.055994
10	7.377	7.369	7.312	7.270	7.344	7.33440	0.044026
20	7.375	7.393	7.338	7.280	7.340	7.34520	0.043309
30	7.377	7.385	7.316	7.308	7.346	7.34640	0.034732
60	7.361	7.402	7.357	7.346	7.370	7.36720	0.021277
120	7.365	7.354	7.362	7.386	7.352	7.36380	0.013535
180	7.427	7.308	7.375	7.397	7.383	7.37800	0.043863
240	7.431	7.355	7.405	7.397	7.353	7.38820	0.033663
300	7.459	7.287	7.391	7.420	7.455	7.40240	0.070227
360		7.289	7.428	7.438	7.460	7.40375	0.077659

Table 48: pH 0.9 Joules

TIME	M219	M227	M231	M233	M239	MEANS	SD
0	7.380	7.484	7.355	7.315	7.317	7.3702	0.069200
1	7.345	7.406	7.278	7.345	7.350	7.3448	0.045373
3	7.241	7.405	7.280	7.369	7.351	7.3292	0.067091
5	7.285	7.432	7.287	7.376	7.344	7.3448	0.062239
10	7.337	7.435	7.300	7.355	7.336	7.3526	0.050203
20	7.406	7.450	7.320	7.360	7.326	7.3724	0.055234
30	7.391	7.477	7.330	7.370	7.315	7.3766	0.063830
60	7.402	7.503	7.330	7.354	7.383	7.3944	0.066636
120	7.511	7.514	7.277	7.328	7.441	7.4142	0.107590
180	7.513	7.513	7.281	7.336	7.461	7.4208	0.106481
240	7.538	7.548	7.269	7.287	7.444	7.4172	0.133543
300	7.535	7.548	7.310	7.348	7.459	7.4400	0.107720
360	7.546	7.547	7.333	7.347	7.451	7.4448	0.103427

Table 49: pH 1.4 Joules

TIME	M225	M228	M234	M237	M243	MEANS	SD
0	7.425	7.333	7.362	7.298	7.402	7.3640	0.051201
1	7.365	7.329	7.264	7.249	7.300	7.3014	0.047311
3	7.321	7.288	7.264	7.227	7.317	7.2834	0.039119
5	7.301	7.332	7.267	7.224	7.309	7.2866	0.042051
10	7.347	7.359	7.263	7.216	7.304	7.2978	0.059386
20	7.413	7.336	7.289	7.248	7.350	7.3272	0.062631
30	7.453	7.372	7.295	7.260	7.338	7.3436	0.074426
60	7.484	7.390	7.314	7.304	7.305	7.3594	0.078344
120	7.505	7.370	7.339	7.361	7.318	7.3786	0.073487
180	7.470	7.359	7.336	7.346	7.359	7.3740	0.054530
240	7.487	7.412	7.317	7.346	7.347	7.3818	0.068321
300	7.505	7.383	7.323	7.365	7.403	7.3958	0.067803
360	7.498	7.368	7.348	7.377	7.417	7.4016	0.059450

Table 50: pH 2.4 Joules

TIME	M220	M223	M236	M241	M244	MEANS	SD
0	7.401	7.370	7.305	7.315	7.377	7.3536	0.041579
1	7.361	7.333	7.271	7.359	7.314	7.3276	0.037146
3	7.341	7.292	7.247	7.399	7.324	7.3206	0.056589
5	7.310	7.228	7.263	7.315	7.357	7.2946	0.049953
10	7.459	7.303	7.250	7.303	7.387	7.3404	0.082473
20	7.491	7.310	7.243	7.266	7.382	7.3384	0.100421
30	7.423	7.326	7.274	7.317	7.420	7.3520	0.066427
60	7.379	7.314	7.300	7.389	7.431	7.3626	0.054601
120	7.248	7.362	7.312	7.481	7.457	7.3720	0.097701
180	7.287	7.424	7.322	7.508	7.473	7.4028	0.095371
240	7.338	7.388	7.322	7.525	7.436	7.4018	0.082123
300	7.411	7.274	7.319	7.523	7.509	7.4072	0.111028
360	7.393		7.286	7.509	7.516	7.4260	0.109054

Figures 75-78: Arterial blood pO_2; controls and cats wounded at 0.9, 1.4 and 2.4 Joules. (means ± S.E. n=5)

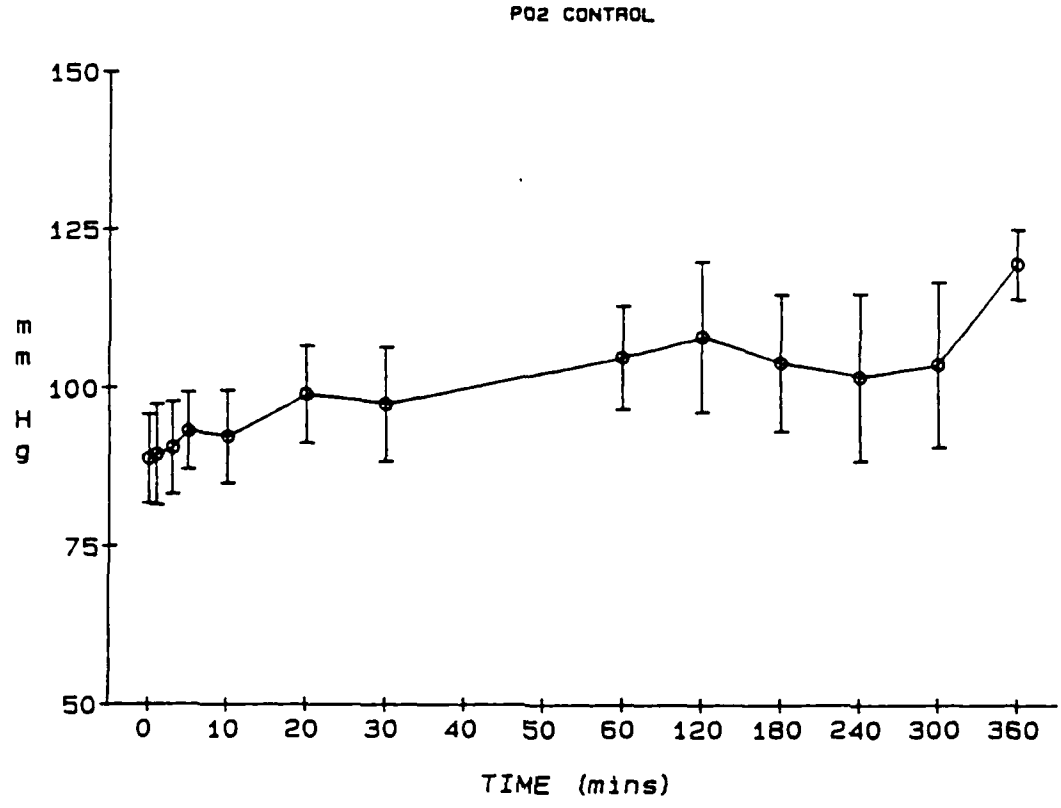


Figure 75

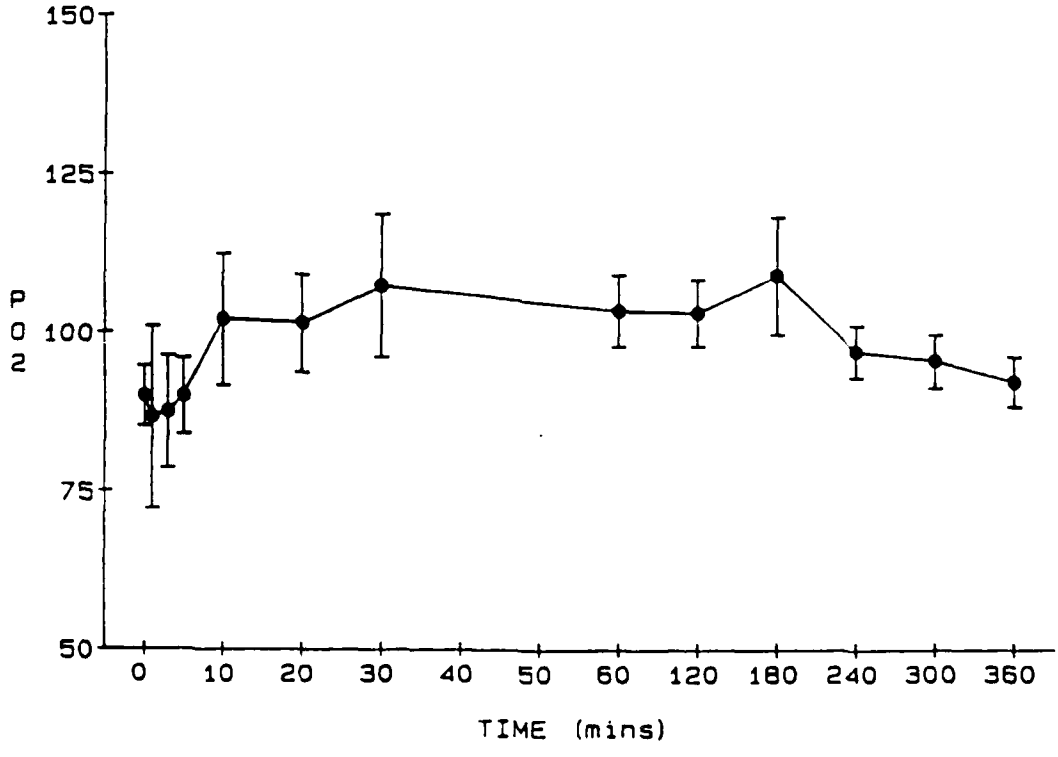


Figure 76

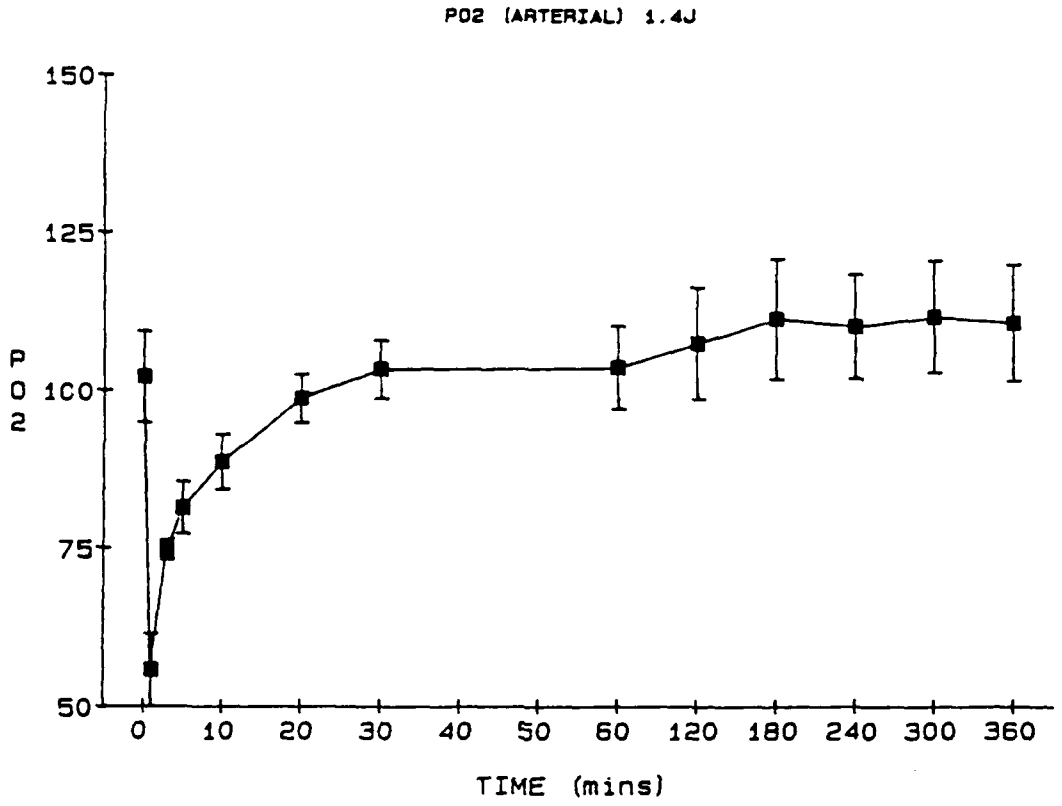


Figure 77

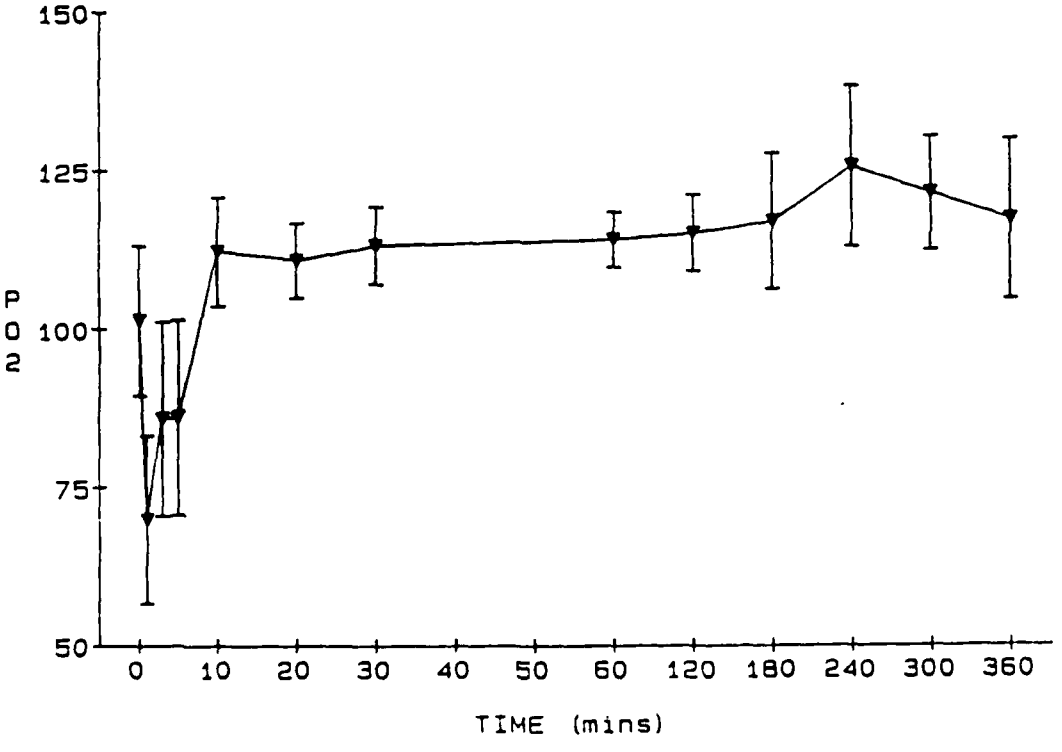


Figure 78

Table 51: PO_2 Control

TIME	C261	C262	C263	C267	C269	MEANS	SD
0	75.0	93.1	73.6	112.3	90.0	88.80	15.761187
1	70.0	92.6	75.2	115.0	94.6	89.48	17.822794
3	71.7	91.0	78.0	112.5	99.3	90.50	16.365971
5	80.2	99.9	79.8	112.3	94.0	93.24	13.773997
10	75.7	100.9	77.1	114.8	93.0	92.30	16.487116
20	81.4	110.0	82.6	121.0	100.1	99.02	17.211392
30	79.5	106.1	76.7	126.1	99.0	97.48	20.315068
60	77.8	112.7	98.5	127.0	108.8	104.96	18.301721
120	77.4	112.5	101.9	150.0	99.2	108.20	26.622641
180	64.2	117.6	111.9	126.7	100.2	104.12	24.295411
240	51.2	121.8	114.7	120.9	100.5	101.82	29.551937
300	53.5	126.8	117.4	118.1	103.3	103.82	29.363191
360		128.7	125.0	121.5	104.0	119.80	10.935874

Table 52: PO_2 0.9 Joules

TIME	M219	M227	M231	M233	M239	MEANS	SD
0	100.0	81.2	82.7	82.6	102.9	89.88	10.628123
1	121.8	63.7	65.7	59.8	121.7	86.54	32.212156
3	64.2	81.5	81.0	92.2	118.0	87.38	19.833104
5	80.5	84.7	78.9	93.0	112.0	89.82	13.549797
10	136.1	84.6	80.1	94.6	114.6	102.00	23.230906
20	127.7	85.5	86.6	99.5	107.4	101.34	17.343097
30	148.0	85.6	87.0	106.5	109.5	107.32	25.223739
60	110.0	88.6	101.2	96.0	121.3	103.42	12.674857
120	120.7	89.7	100.6	96.8	107.7	103.10	11.794278
180	144.5	93.0	108.7	95.7	103.3	109.04	20.770845
240	111.5	94.0	100.3	88.7	90.7	97.04	9.202065
300	91.7	88.6	110.7	98.7	88.1	95.56	9.461395
360	91.4	87.8	107.6	89.2	85.3	92.26	8.856523

Table 53: PO_2 1.4 Joules

TIME	M225	M228	M234	M237	M243	MEANS	SD
0	101.6	74.3	109.8	113.6	111.4	102.14	16.210429
1	59.4	71.7	39.3	46.8	61.2	55.68	12.728983
3	71.7	74.2	80.1	75.7	71.6	74.66	3.500429
5	81.0	85.0	87.8	87.3	65.5	81.32	9.242132
10	95.4	79.0	94.2	97.6	77.0	88.64	9.814683
20	101.2	83.8	105.3	99.8	103.4	98.70	8.589529
30	112.5	86.0	108.6	107.3	101.8	103.24	10.371258
60	95.2	95.7	118.3	120.5	88.2	103.58	14.763367
120	89.8	94.6	124.4	133.3	94.9	107.40	19.935270
180	93.0	89.4	127.6	138.2	108.1	111.26	21.295727
240	98.1	91.3	126.0	133.4	101.9	110.14	18.441611
300	94.0	88.3	129.0	132.0	115.0	111.66	19.894170
360	93.3	87.4	132.0	131.1	109.9	110.74	20.713112

Table 54: PO_2 2.4 Joules

TIME	M220	M223	M236	M241	M244	MEANS	SD
0	60.8	127.5	91.5	105.8	120.6	101.240	26.530417
1	47.1	120.0	51.5	57.9	72.9	69.880	29.670726
3	40.7	87.2	65.1	127.2	108.6	85.760	34.271898
5	29.4	86.5	86.8	114.3	113.1	86.020	34.422914
10	101.7	128.2	83.3	122.0	125.7	112.180	19.233746
20	106.1	123.5	95.2	103.3	125.7	110.760	13.275843
30	104.4	120.6	96.4	112.5	131.7	113.120	13.758161
60	106.5	115.0	104.3	115.4	129.0	114.040	9.724865
120	100.8	125.9	105.6	110.5	132.3	115.020	13.493962
180	118.0	146.5	84.7	103.3	132.0	116.900	24.120427
240	168.2	140.0	110.6	98.6	110.0	125.480	28.369914
300	144.3	122.6	102.1	99.7	137.4	121.220	20.156066
360	136.3		87.5	104.5	140.0	117.075	25.350657

Figures 79-82: Arterial blood glucose; controls and cats wounded at 0.9, 1.4 and 2.4 Joules. (means ± S.E. n=5)

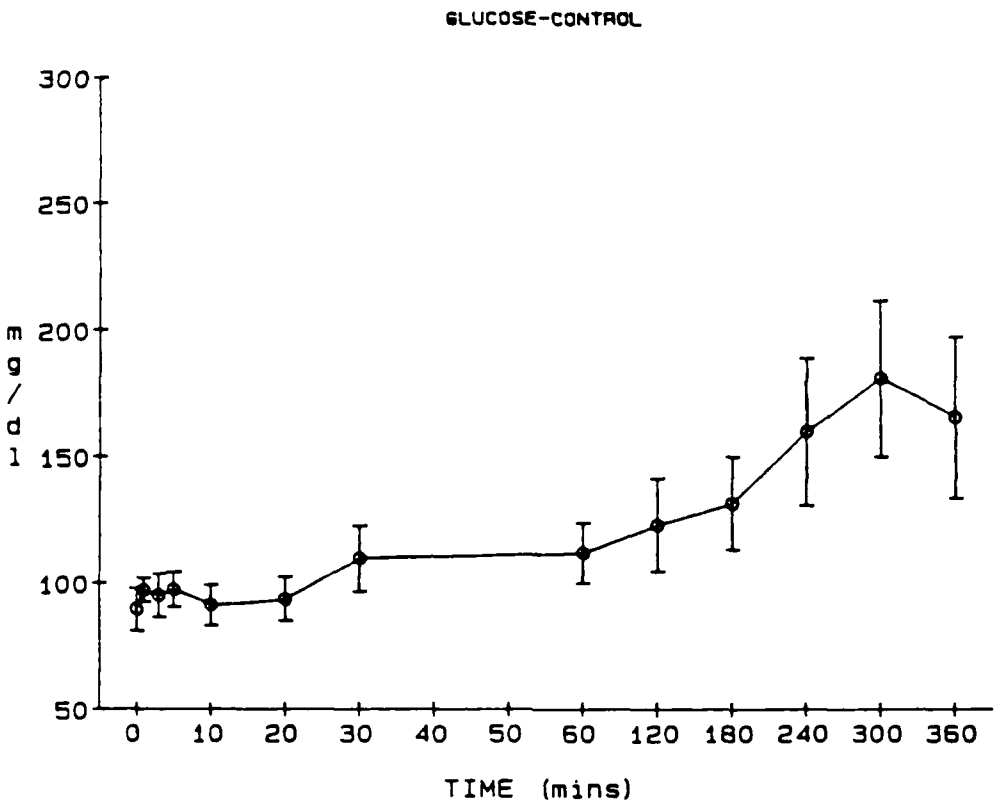


Figure 79

GLUCOSE

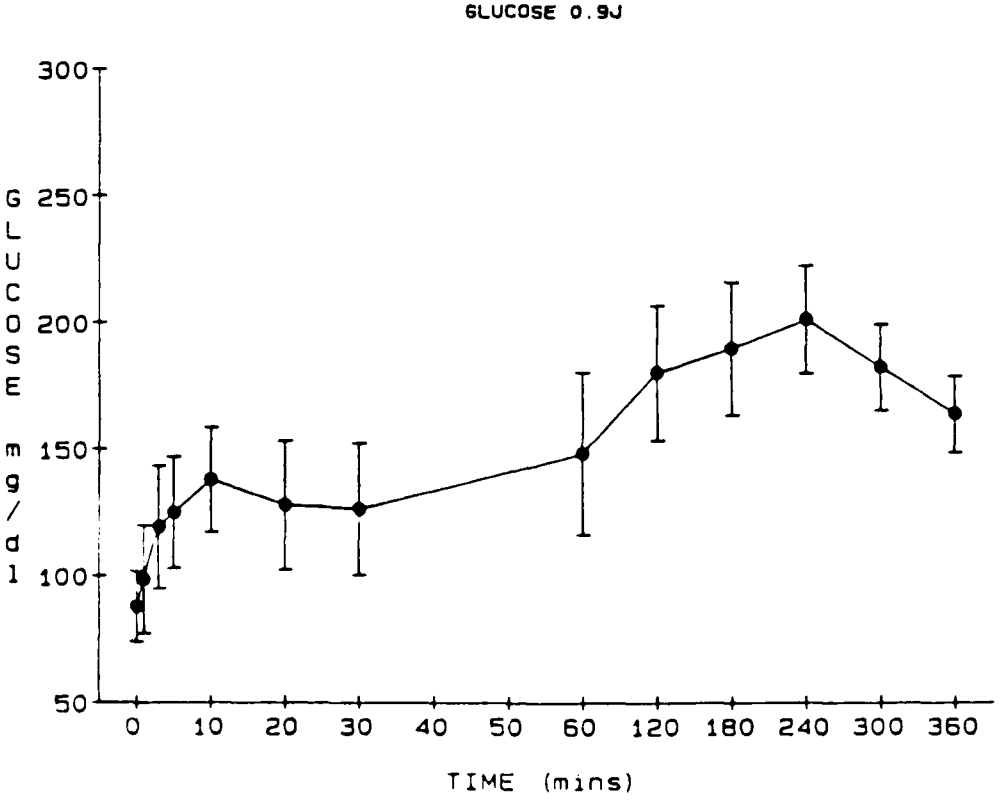


Figure 80

GLUCOSE

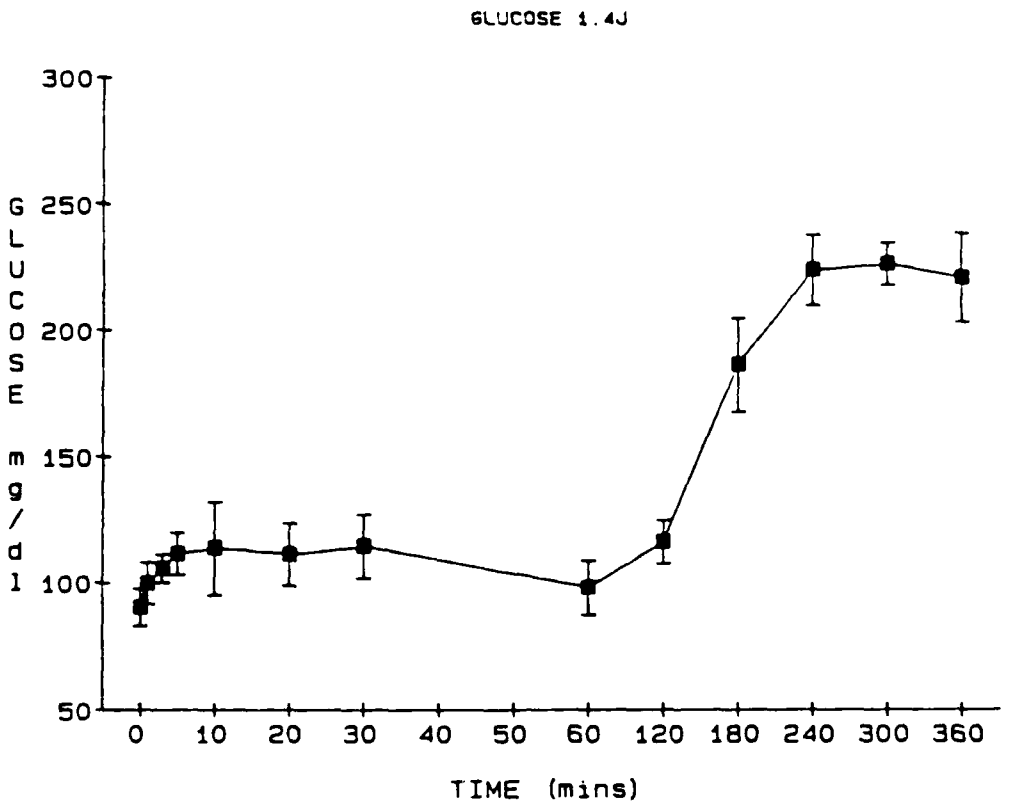


Figure 81

GLUCOSE

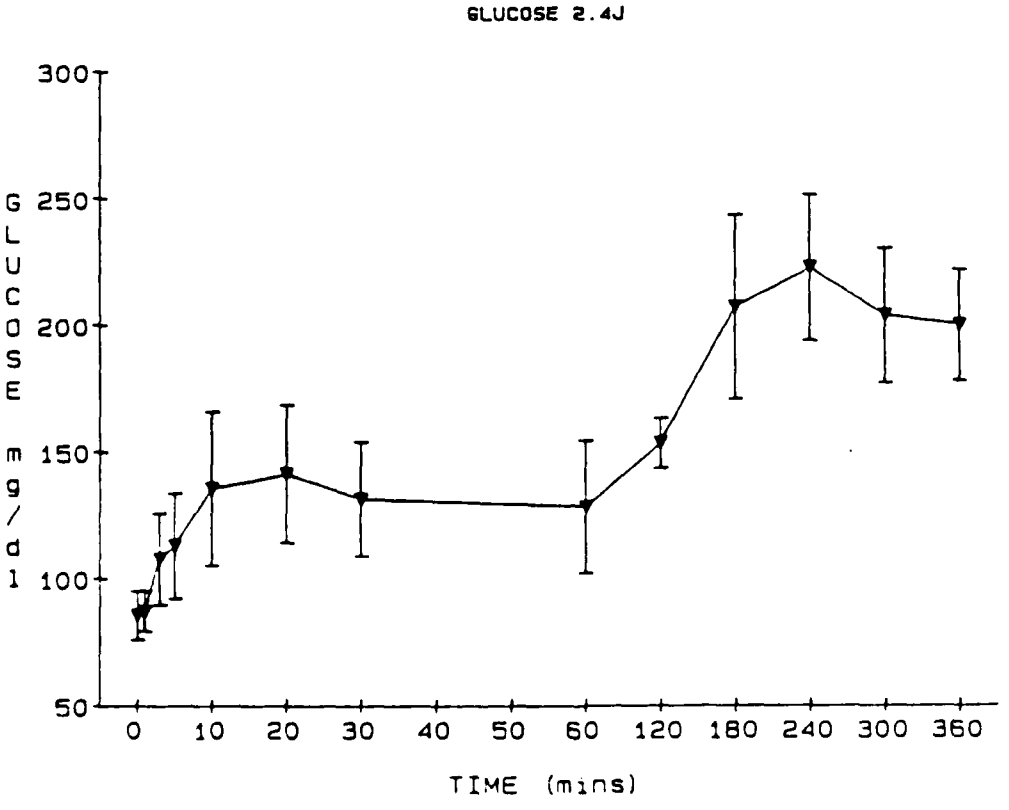


Figure 82

GLUCOSE

Table 55: Glucose Control

TIME	C261	C262	C263	C267	C269	MEANS	SD
0	80	107	101	98	61	89.4	18.796276
1	84	110	104	99	89	97.2	10.663020
3	90	124	94	96	71	95.0	19.000000
5	104	112	104	95	72	97.4	15.420765
10	90	96	102	107	61	91.2	18.047160
20	96	96	113	102	61	93.6	19.501282
30	132	130	120	105	61	109.6	29.194178
60	127	134	115	117	66	111.8	26.733874
120	132	170	148	98	66	122.8	41.197087
180	99	177	174	116	91	131.4	41.271055
240	95	254	184	164	102	159.8	65.224229
300	97	285	147	198	178	181.0	69.508992
360	88	259	106	164	211	165.6	71.346338

Table 56: Glucose 0.9 Joules

TIME	M219	M227	M231	M233	M239	MEANS	SD
0	66	130	65	65	112	87.6	31.149639
1	64	169	65	67	127	98.4	47.663403
3	104	210	68	93	120	119.0	54.277067
5	96	208	81	121	118	124.8	49.322409
10	94	212	107	149	127	137.8	46.407973
20	78	219	84	138	120	127.8	56.746806
30	78	226	96	107	124	126.2	58.242596
60	89	236	129	76	210	148.0	71.787882
120	171	235	197	82	215	180.0	59.632206
180	186	243	225	92	202	189.6	58.730742
240	224	219	227	116	220	201.2	47.735731
300	199	205	204	115	188	182.2	38.166739
360	132	187	210	153	136	163.6	33.812720

Table 57: Glucose 1.4 Joules

TIME	M225	M228	M234	M237	M243	MEANS	SD
0	90	72	76	106	107	90.2	16.315637
1	95	76	93	125	110	99.8	18.539148
3	105	85	113	118	107	105.6	12.601587
5	111	85	137	116	108	111.4	18.609138
10	180	73	96	123	95	113.4	41.234694
20	120	77	90	146	123	111.2	27.598913
30	111	92	84	153	132	114.4	28.448199
60	100	71	84	135	100	98.0	23.989581
120	120	129	113	134	85	116.2	19.227584
180	219	183	233	167	129	186.2	41.583651
240	242	201	262	229	185	223.8	30.995161
300	201	230	252	232	217	226.4	18.928814
360	170	232	252	190	261	221.0	39.509493

Table 58: Glucose 2.4 Joules

TIME	M220	M223	M236	M241	M244	MEANS	SD
0	81	76	64	121	86	85.6	21.407942
1	76	79	72	115	94	87.2	17.626684
3	85	100	78	178	98	107.8	40.288956
5	73	120	84	190	98	113.0	46.486557
10	87	121	94	253	123	135.6	67.541099
20	87	119	107	241	153	141.4	60.620129
30	78	98	112	193	176	131.4	50.316995
60	78	84	95	188	196	128.2	58.627639
120	160	168	121	142	176	153.4	22.063545
180	180	346	204	136	170	207.2	81.346174
240	239	305	254	154	161	222.6	64.314073
300	167	283	251	152	166	203.8	59.090608
360	204		254	195	147	200.0	43.840620

Figures 83-86: Hematocrit; controls and cats wounded at 0.9, 1.4 and 2.4 Joules. (means ± S.E. n=5)

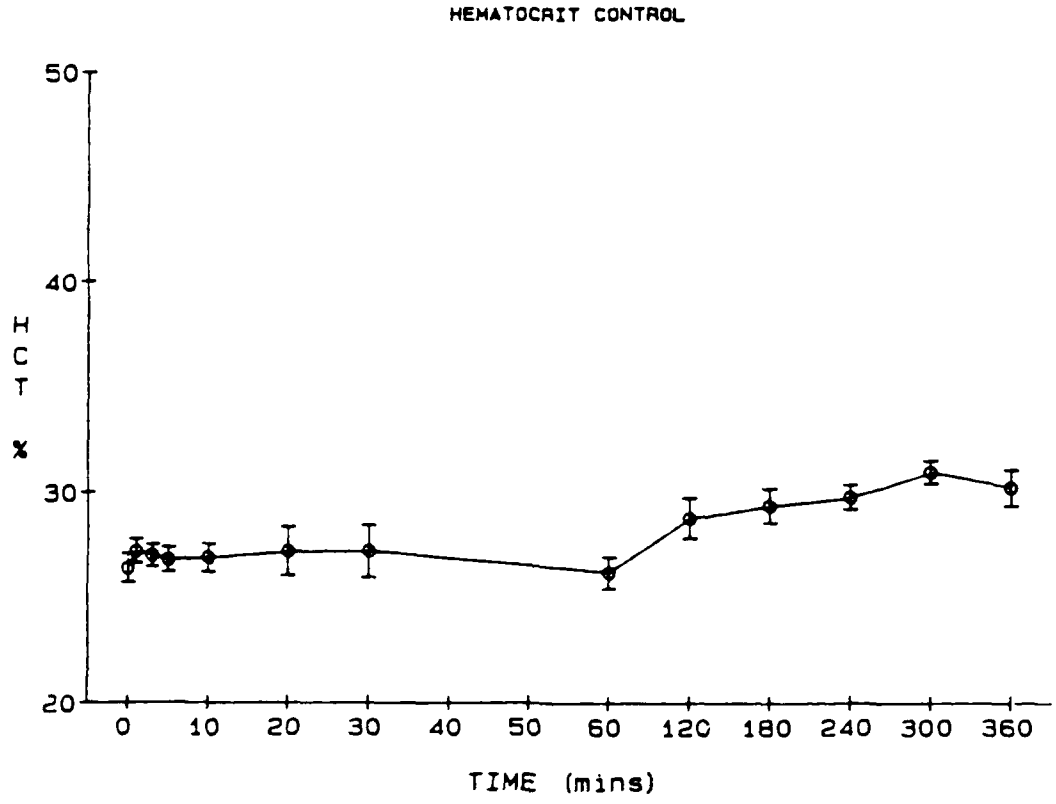


Figure 83

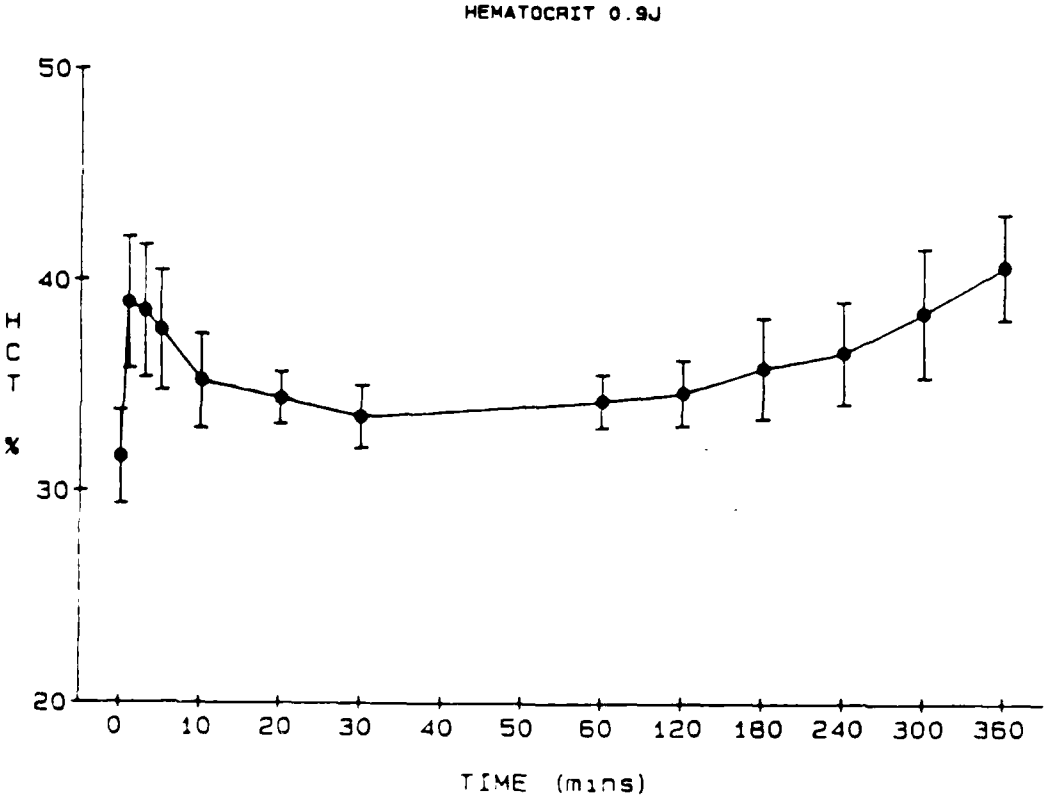


Figure 84

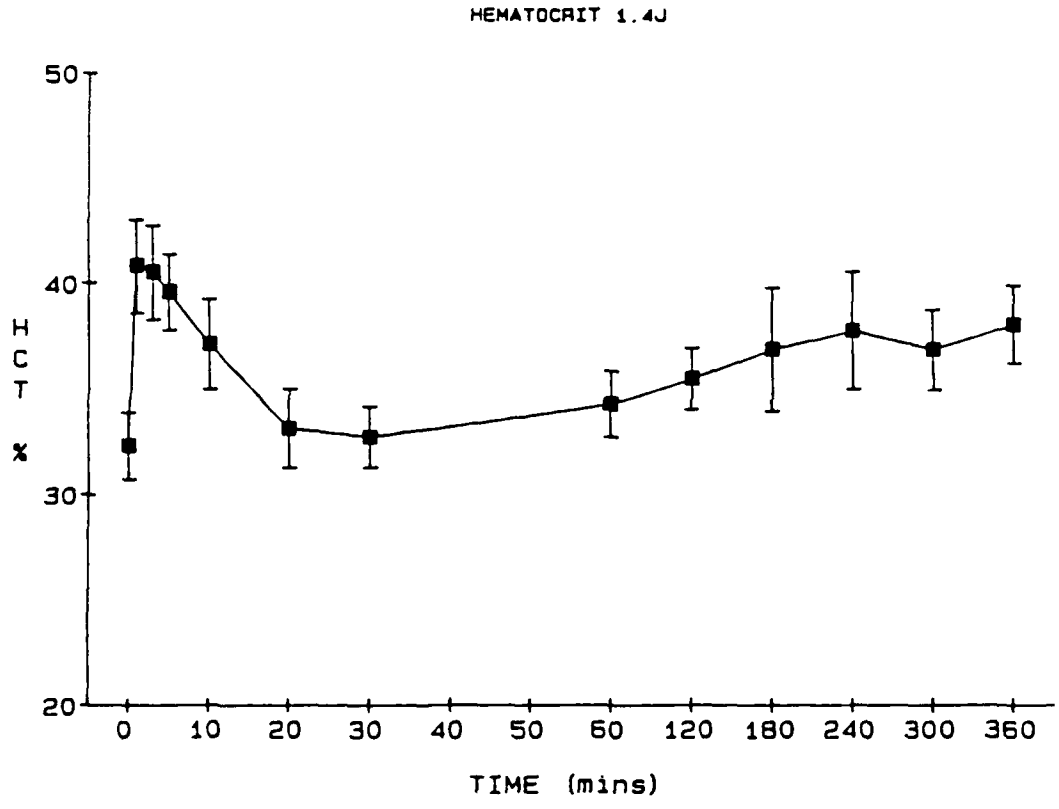


Figure 85

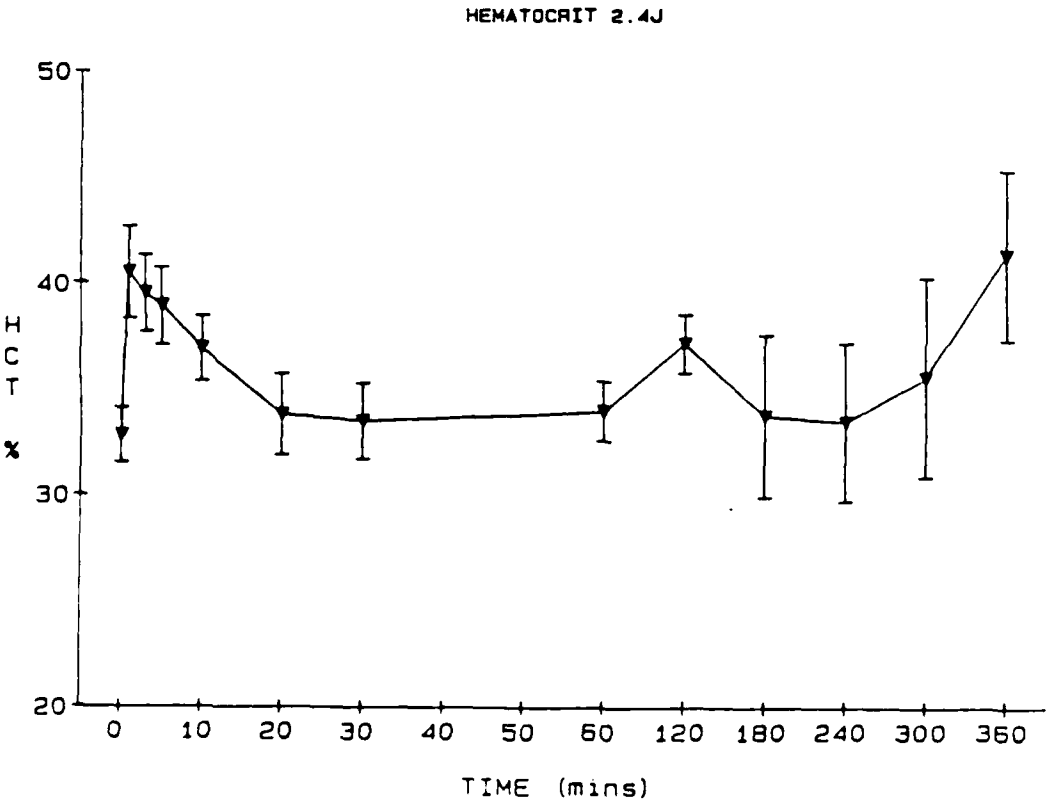


Figure 86

Table 59: Hematocrit Control

TIME	C261	C262	C263	C267	C269	MEANS	SD
0	26.0	26	29	25	26	26.40	1.516575
1	28.0	26	29	26	27	27.20	1.303840
3	28.0	27	28	25	27	27.00	1.224745
5	28.0	26	28	25	27	26.80	1.303840
10	27.5	26	29	25	27	26.90	1.516575
20	28.0	25	29	24	30	27.20	2.588436
30	28.0	25	28	24	31	27.20	2.774887
60	27.0	25	27	24	28	26.20	1.643168
120	27.0	28	32	27	30	28.80	2.167948
180	27.0	29	32	30	29	29.40	1.816590
240	28.0	29	30	31	31	29.80	1.303840
300	29.0	32	32	31	31	31.00	1.224745
360	28.0		32	30	31	30.25	1.707825

Table 60: Hematocrit 0.9 Joules

TIME	M219	M227	M231	M233	M239	MEANS	SD
0	34.0	28.0	39.0	30.0	27	31.6	4.929503
1	45.0	41.0	39.5	42.0	27	38.9	6.949820
3	46.0	39.0	39.5	41.0	27	38.5	7.000000
5	44.0	38.0	39.5	39.5	27	37.6	6.338375
10	41.0	32.5	37.5	37.0	28	35.2	5.032395
20	37.0	31.5	37.5	32.0	34	34.4	2.770379
30	36.5	31.5	37.5	30.0	32	33.5	3.297726
60	36.0	34.0	37.5	30.0	34	34.3	2.819574
120	37.0	38.0	36.5	30.0	32	34.7	3.492850
180	41.0	41.5	36.0	30.0	31	35.9	5.389805
240	42.0	41.5	37.5	32.0	30	36.6	5.447476
300	48.0	42.5	38.0	32.0	32	38.5	6.910137
360	47.0	42.5	43.0	32.0	39	40.7	5.630275

Table 61: Hematocrit 1.4 Joules

TIME	M225	M228	M234	M237	M243	MEANS	SD
0	28.0	31.5	32.0	38.0	32	32.30	3.598611
1	43.5	47.0	35.5	42.0	36	40.80	4.957318
3	42.5	47.5	35.5	41.0	36	40.50	4.962358
5	39.8	46.0	35.5	39.5	37	39.56	4.017835
10	33.0	43.5	32.0	40.0	37	37.10	4.801042
20	29.0	33.5	32.0	40.0	31	33.10	4.189272
30	29.5	33.0	32.0	38.0	31	32.70	3.232646
60	29.5	35.0	32.0	37.0	38	34.30	3.528456
120	33.5	33.0	33.0	40.0	38	35.50	3.278719
180	33.5	31.5	32.5	47.0	40	36.90	6.551717
240	33.5	31.5	36.0	47.0	41	37.80	6.251000
300	33.5	31.5	40.0	41.5	38	36.90	4.263215
360	36.0	32.0	41.5	39.0	42	38.10	4.159327

Table 62: Hematocrit 2.4 Joules

TIME	M220	M223	M236	M241	M244	MEANS	SD
0	33.0	29.5	32	37.5	32	32.800	2.928310
1	42.0	38.5	39	48.0	35	40.500	4.873397
3	42.0	36.5	39	45.0	35	39.500	4.062019
5	42.0	36.5	38	44.0	34	38.900	4.068169
10	40.0	32.5	38	40.0	34	36.900	3.471311
20	31.0	29.0	36	40.0	33	33.800	4.324350
30	30.0	29.5	36	39.0	33	33.500	4.031129
60	32.0	31.0	35	39.0	33	34.000	3.162278
120	41.0	35.0	36	40.0	34	37.200	3.114482
180	31.0	20.0	39	41.0	38	33.800	8.584870
240	30.0	20.5	39	41.0	37	33.500	8.366600
300	29.5	20.5	40	47.0	41	35.600	10.532094
360	31.5		40	51.0	43	41.375	8.055795

Table 63

LESIONED HEMISPHERE - WHITE MATTER

		%WATER	Na^+ (mEq/Kg dry weight)	K^+ (mEq/Kg dry weight)
0 HOUR				
CONTROL	mean	65.22	147.36	253.14
(4)	S.D.	2.09	6.03	13.86
6 HOUR				
CONTROL	mean	66.43	157.25	264.12
(4)	S.D.	2.30	12.27	22.55
0.9J	mean	67.71	186.78	251.65
(4)	S.D.	1.37	37.71	19.93
1.4J	mean	68.19	173.76	256.30
(4)	S.D.	2.95	13.74	27.89
24 HOUR				
CONTROL	mean	66.10	155.20	261.15
(4)	S.D.	1.90	7.87	16.60
0.9J	mean	73.61**	252.79**	280.26
(4)	S.D.	2.48	32.07	56.75
1.4J	mean	68.91	215.15*	218.75
(4)	S.D.	1.61	44.23	33.43
48 HOUR				
CONTROL	mean	66.05	146.05	234.47
(4)	S.D.	1.14	24.70	29.84
0.9J	mean	68.60+	234.71**	221.79
(4)	S.D.	2.05	40.26	19.54
1.4J	mean	72.26*	254.07*	254.12
(4)	S.D.	3.51	57.27	35.65
ROD	mean	65.93	161.10	260.80
(4)	S.D.	2.70	23.60	23.13
72 HOUR				
CONTROL	mean	65.03	160.42	253.33
(4)	S.D.	1.67	23.26	23.41
0.9J	mean	68.96*	210.43*	233.39
(3)	S.D.	1.86	15.67	25.41
1.4J	mean	68.53*	216.71*	224.94
(4)	S.D.	1.56	29.94	24.71
168 HOUR				
CONTROL	mean	67.11	156.43	276.72
(5)	S.D.	2.45	5.28	16.65
0.9J	mean	67.37	188.59*	253.18
(5)	S.D.	1.48	15.59	11.23
1.4J	mean	65.82	203.20*	213.11*
(5)	S.D.	4.10	36.72	14.37
ROD	mean	66.39	162.38	272.07
(4)	S.D.	2.43	12.25	20.16

** $P<0.01$, * $P<0.05$ as compared to corresponding time control values.
+ $P<0.05$ comparing 0.9J and 1.4J values.

Table 64

NON-LESIONED HEMISPHERE - WHITE MATTER

		%WATER	Na^+ (mEq/Kg dry weight)	K^+ (mEq/Kg dry weight)
0 HOUR				
CONTROL	mean	65.23	145.49	255.78
(4)	S.D.	2.04	8.23	15.52
6 HOUR				
CONTROL	mean	63.88	143.54	236.42
(4)	S.D.	2.73	7.42	16.77
0.9J	mean	64.67	140.69	265.12
(4)	S.D.	3.24	9.86	27.97
1.4J	mean	67.54	157.93	261.32
(4)	S.D.	2.63	15.40	29.40
24 HOUR				
CONTROL	mean	67.04	158.55	270.27
(4)	S.D.	1.41	8.91	18.50
0.9J	mean	68.50	156.76	278.20
(4)	S.D.	2.18	10.96	26.57
1.4J	mean	66.14	150.93	247.10
(4)	S.D.	1.27	14.93	22.10
48 HOUR				
CONTROL	mean	64.12	148.70	238.98
(4)	S.D.	1.43	9.31	27.26
0.9J	mean	64.49	154.97	243.68
(4)	S.D.	1.01	12.84	10.74
1.4J	mean	65.62	150.14	246.93
(4)	S.D.	3.28	13.70	26.08
ROD	mean	63.48	149.64	249.33
(4)	S.D.	5.41	34.16	36.42
72 HOUR				
CONTROL	mean	64.04	149.16	226.14
(4)	S.D.	1.81	19.99	9.25
0.9J	mean	65.61	169.91	239.88
(3)	S.D.	0.37	12.14	24.87
1.4J	mean	65.94	154.93	252.47
(4)	S.D.	2.86	19.79	24.36
168 HOUR				
CONTROL	mean	65.93	149.77	273.09
(5)	S.D.	2.22	12.77	37.60
0.9J	mean	64.47	159.59	252.28
(5)	S.D.	2.28	16.77	13.27
1.4J	mean	64.23	161.66	246.08
(5)	S.D.	3.75	11.91	34.25
ROD	mean	64.85	154.13	266.27
(4)	S.D.	2.33	13.97	26.89

No significant differences.

Table 65

LESIONED HEMISPHERE - FRONTAL CORTEX

		%WATER	Na^+ (mEq/Kg dry weight)	K^+ (mEq/Kg dry weight)
0 HOUR				
CONTROL	mean	77.62	220.36	443.82
(4)	S.D.	0.38	6.60	5.41
6 HOUR				
CONTROL	mean	77.61	220.23	448.28
(4)	S.D.	0.41	5.27	16.69
0.9J	mean	78.99	275.85*	410.58*
(4)	S.D.	1.30	42.96	15.32
1.4J	mean	78.45	249.92	396.41*
(4)	S.D.	1.42	34.36	24.88
24 HOUR				
CONTROL	mean	78.09	223.17	450.54
(4)	S.D.	1.16	8.84	29.95
0.9J	mean	78.10	249.41	412.29
(4)	S.D.	0.93	22.08	33.74
1.4J	mean	78.01	257.45*	409.51
(4)	S.D.	0.73	25.80	59.74
48 HOUR				
CONTROL	mean	77.16	231.15	434.30
(4)	S.D.	1.01	19.70	27.27
0.9J	mean	77.29	281.19**	366.14*
(4)	S.D.	1.52	14.62	26.03
1.4J	mean	78.54	254.80	410.28
(4)	S.D.	1.42	40.51	31.74
ROD	mean	77.40	230.17	424.80
(4)	S.D.	1.58	30.07	30.67
72 HOUR				
CONTROL	mean	76.10	219.66	404.69
(4)	S.D.	2.34	41.15	44.60
0.9J	mean	78.06	264.40	408.92
(3)	S.D.	1.53	41.63	20.12
1.4J	mean	78.86*	261.78	424.32
(4)	S.D.	0.48	31.38	32.71
168 HOUR				
CONTROL	mean	77.72	232.00	463.79
(5)	S.D.	0.88	15.40	18.04
0.9J	mean	77.93	254.81	431.31*
(5)	S.D.	0.95	20.64	23.42
1.4J	mean	78.12	269.42**	433.00*
(5)	S.D.	0.91	9.84	22.86
ROD	mean	76.14	223.85	408.03
(4)	S.D.	2.29	15.61	57.83

** $P<0.01$, * $P<0.05$ as compared to corresponding time control values.

Table 66

NON-LESIONED HEMISPHERE - FRONTAL CORTEX

		%WATER	Na^+ (mEq/Kg dry weight)	K^+ (mEq/Kg dry weight)
0 HOUR				
CONTROL	mean	77.93	221.68	454.45
(4)	S.D.	0.37	2.40	12.92
6 HOUR				
CONTROL	mean	79.00	231.83	469.25
(4)	S.D.	1.44	24.03	51.02
0.9J	mean	77.15	212.06	422.71
(4)	S.D.	0.96	15.31	23.87
1.4J	mean	77.58	210.45	434.77
(4)	S.D.	0.82	8.00	18.74
24 HOUR				
CONTROL	mean	78.21	225.84	450.63
(4)	S.D.	1.12	13.86	29.22
0.9J	mean	78.02	209.69	457.29
(4)	S.D.	1.12	5.88	30.93
1.4J	mean	76.72	205.15	422.44
(4)	S.D.	1.70	26.10	60.29
48 HOUR				
CONTROL	mean	76.93	227.68	424.66
(4)	S.D.	0.93	20.72	31.72
0.9J	mean	76.00	210.72	402.05
(4)	S.D.	1.02	16.71	24.25
1.4J	mean	77.93	219.16	436.36
(4)	S.D.	2.06	24.89	44.99
ROD	mean	77.23	212.44	419.98
(4)	S.D.	0.87	22.69	49.85
72 HOUR				
CONTROL	mean	76.76	226.96	416.17
(4)	S.D.	0.65	25.94	12.70
0.9J	mean	76.35	215.67	404.22
(3)	S.D.	1.02	13.91	16.86
1.4J	mean	78.50**	231.27	426.87
(4)	S.D.	0.63	9.62	42.77
168 HOUR				
CONTROL	mean	77.46	227.68	446.10
(5)	S.D.	0.36	6.51	21.20
0.9J	mean	76.64	226.81	434.68
(5)	S.D.	1.17	21.34	28.70
1.4J	mean	77.04	243.20	460.97
(5)	S.D.	1.59	20.37	42.54
ROD	mean	75.61	209.25	410.71
(4)	S.D.	2.17	30.19	35.83

** $P<0.01$ as compared to corresponding time control values.

Table 67

LESIONED HEMISPHERE - ANTERIOR PARIETAL CORTEX

		%WATER	Na^+ (mEq/Kg dry weight)	K^+ (mEq/Kg dry weight)
0 HOUR				
CONTROL	mean	77.49	217.41	441.34
(4)	S.D.	0.64	4.94	13.61
6 HOUR				
CONTROL	mean	74.14	191.39	374.37
(4)	S.D.	0.99	5.75	15.24
0.9J	mean	76.47*	214.97*	392.66
(4)	S.D.	1.05	15.12	26.01
1.4J	mean	76.82*	217.00**	399.81
(4)	S.D.	1.75	18.60	27.39
24 HOUR				
CONTROL	mean	78.20	226.34	451.93
(4)	S.D.	0.51	6.92	10.68
0.9J	mean	77.70	221.06	419.73
(4)	S.D.	1.12	19.46	42.39
1.4J	mean	77.33	227.37	406.21
(4)	S.D.	1.20	27.00	39.02
48 HOUR				
CONTROL	mean	73.98	201.91	372.34
(4)	S.D.	1.21	17.86	32.86
0.9J	mean	77.58**	273.28**	374.83
(4)	S.D.	0.78	9.32	20.19
1.4J	mean	77.54*	219.70++	421.92
(4)	S.D.	1.59	12.35	33.76
ROD	mean	74.95	213.14	376.44
(4)	S.D.	1.00	17.18	26.82
72 HOUR				
CONTROL	mean	75.21	202.57	388.98
(4)	S.D.	1.26	18.41	27.53
0.9J	mean	75.73	244.51*	365.59
(3)	S.D.	1.14	2.65	28.45
1.4J	mean	78.62*	242.64	404.50
(4)	S.D.	0.58	30.68	25.27
168 HOUR				
CONTROL	mean	76.09	207.93	421.48
(5)	S.D.	0.90	5.59	15.93
0.9J	mean	76.13	232.66	398.00
(5)	S.D.	0.96	23.45	34.64
1.4J	mean	77.16	266.83**	402.07
(5)	S.D.	1.90	25.55	58.39
ROD	mean	75.13	216.08	375.66#
(4)	S.D.	1.32	18.77	22.74

** P<0.01, * P<0.05 as compared to corresponding time control values.
++ P<0.01 comparing 0.9J and 1.4J values. # P<0.05 comparing rod value with corresponding time control value.

Table 68

NON-LESIONED HEMISPHERE - ANTERIOR PARIETAL CORTEX

		%WATER	Na^+ (mEq/Kg dry weight)	K^+ (mEq/Kg dry weight)
0 HOUR				
CONTROL	mean	77.72	218.25	445.04
(4)	S.D.	0.64	6.05	12.59
6 HOUR				
CONTROL	mean	75.26	196.05	389.09
(4)	S.D.	1.11	9.80	23.57
0.9J	mean	75.07	187.02	386.71
(4)	S.D.	1.02	5.64	21.06
1.4J	mean	77.06*	197.20	419.67
(4)	S.D.	0.96	17.43	29.70
24 HOUR				
CONTROL	mean	77.32	215.40	431.15
(4)	S.D.	0.40	7.84	10.59
0.9J	mean	76.28	193.31*	414.25
(4)	S.D.	1.32	9.09	39.24
1.4J	mean	76.72	183.42**	398.01*
(4)	S.D.	0.99	7.84	19.85
48 HOUR				
CONTROL	mean	74.99	207.77	390.08
(4)	S.D.	1.70	22.81	38.34
0.9J	mean	74.45	192.94	369.89
(4)	S.D.	0.56	8.27	5.26
1.4J	mean	77.04	207.21	421.61
(4)	S.D.	1.80	15.29	26.20
ROD	mean	74.01	193.02	372.22
(4)	S.D.	0.70	8.95	16.65
72 HOUR				
CONTROL	mean	74.35	194.79	369.33
(4)	S.D.	2.15	22.30	39.60
0.9J	mean	75.39	206.85	401.89
(3)	S.D.	2.04	23.49	40.68
1.4J	mean	76.70	208.80	408.67
(4)	S.D.	0.92	6.79	20.63
168 HOUR				
CONTROL	mean	77.04	212.79	434.00
(5)	S.D.	0.60	10.40	19.16
0.9J	mean	76.24	224.18	428.70
(5)	S.D.	1.64	20.43	39.75
1.4J	mean	75.41	216.97	408.42
(5)	S.D.	1.91	21.63	42.42
ROD	mean	75.68	206.54	409.25
(4)	S.D.	1.68	10.89	36.49

** $P<0.01$, * $P<0.05$ as compared to corresponding time control values.

Table 69

LESIONED HEMISPHERE - POSTERIOR PARIETAL CORTEX

		%WATER	Na^+ (mEq/Kg dry weight)	K^+
0 HOUR				
CONTROL	mean	77.05	214.40	430.45
(4)	S.D.	0.66	10.01	17.56
6 HOUR				
CONTROL	mean	75.38	200.47	396.84
(4)	S.D.	2.44	19.58	43.48
0.9J	mean	76.90	225.59	397.75
(4)	S.D.	0.91	35.32	30.10
1.4J	mean	77.25	215.97	410.84
(4)	S.D.	0.89	18.38	26.45
24 HOUR				
CONTROL	mean	77.35	219.65	428.29
(4)	S.D.	0.46	6.57	18.29
0.9J	mean	77.82	223.49	435.88
(4)	S.D.	1.64	9.66	44.54
1.4J	mean	76.89	220.00	388.34
(4)	S.D.	1.00	10.84	24.40
48 HOUR				
CONTROL	mean	75.19	209.53	391.75
(4)	S.D.	0.74	14.94	24.04
0.9J	mean	77.37*	263.02*	374.82
(4)	S.D.	1.05	30.92	22.47
1.4J	mean	76.41	209.18	393.96
(4)	S.D.	1.30	16.23	38.84
ROD	mean	75.20	200.21	382.59
(4)	S.D.	0.82	6.30	24.82
72 HOUR				
CONTROL	mean	74.28	200.66	366.33
(4)	S.D.	0.96	12.15	16.81
0.9J	mean	76.46	236.00	382.25
(3)	S.D.	1.95	19.21	55.20
1.4J	mean	77.84**	244.08	395.05
(4)	S.D.	0.86	36.76	36.35
168 HOUR				
CONTROL	mean	76.65	214.10	432.62
(5)	S.D.	0.50	6.90	14.14
0.9J	mean	76.06	239.40*	401.99*
(5)	S.D.	0.91	23.46	25.74
1.4J	mean	77.47	257.65**	418.45
(5)	S.D.	0.91	19.63	26.77
ROD	mean	76.17	215.27	405.75#
(4)	S.D.	0.62	14.59	16.47

** $P<0.01$, * $P<0.05$ as compared to corresponding time control values.
# $P<0.05$ comparing rod value with corresponding time control value.

Table 70

NON-LESIONED HEMISPHERE - POSTERIOR PARIETAL CORTEX

		%WATER	Na^+ (mEq/Kg dry weight)	K^+
0 HOUR				
CONTROL	mean	77.46	218.90	439.51
(4)	S.D.	1.29	10.39	29.29
6 HOUR				
CONTROL	mean	76.06	207.61	406.83
(4)	S.D.	0.38	2.50	12.34
0.9J	mean	75.70	194.24	395.96
(4)	S.D.	1.01	16.62	23.05
1.4J	mean	76.30	201.03	402.65
(4)	S.D.	1.17	18.45	15.71
24 HOUR				
CONTROL	mean	76.92	215.00	420.06
(4)	S.D.	0.61	9.05	23.27
0.9J	mean	76.89	205.44	421.62
(4)	S.D.	1.17	11.51	25.56
1.4J	mean	75.93	193.34	409.90
(4)	S.D.	1.87	19.84	50.23
48 HOUR				
CONTROL	mean	75.27	206.79	387.95
(4)	S.D.	0.67	13.06	20.00
0.9J	mean	74.90	200.08	377.06
(4)	S.D.	1.25	12.37	20.01
1.4J	mean	76.08	185.73	359.41
(4)	S.D.	1.44	29.70	62.82
ROD	mean	73.62	188.16#	362.84
(4)	S.D.	1.25	5.63	21.01
72 HOUR				
CONTROL	mean	73.82	188.88	352.88
(4)	S.D.	1.30	10.56	21.82
0.9J	mean	74.08	195.45	368.67
(3)	S.D.	1.75	14.01	32.87
1.4J	mean	76.09*	201.49*	397.99*
(4)	S.D.	0.95	7.12	19.09
168 HOUR				
CONTROL	mean	77.26	226.18	452.42
(5)	S.D.	0.54	10.93	14.08
0.9J	mean	75.14**	214.35	400.06**
(5)	S.D.	0.97	12.78	12.08
1.4J	mean	77.46	236.42	451.62
(5)	S.D.	1.08	12.91	30.30
ROD	mean	75.51#	207.55#	405.06##
(4)	S.D.	1.06	.09	12.18

** P<0.01, * P<0.05 as compared to corresponding time control values.
P<0.01, # P<0.05 comparing rod value with corresponding time control value.

Table 71

LESIONED HEMISPHERE - OCCIPITAL CORTEX

		%WATER	Na^+ (mEq/Kg dry weight)	K^+
0 HOUR				
CONTROL	mean	78.13	232.54	452.51
(4)	S.D.	0.72	6.83	22.91
6 HOUR				
CONTROL	mean	77.47	227.59	427.97
(4)	S.D.	1.32	10.92	30.64
0.9J	mean	78.13	275.24	386.46
(4)	S.D.	2.35	44.00	20.63
1.4J	mean	78.79	276.79	393.98
(4)	S.D.	1.70	40.55	7.28
24 HOUR				
CONTROL	mean	78.45	237.07	458.41
(4)	S.D.	0.69	5.90	12.52
0.9J	mean	78.39	281.32*	384.92**
(4)	S.D.	1.43	26.71	24.14
1.4J	mean	78.87	314.13**	361.30**
(4)	S.D.	0.26	29.25	39.79
48 HOUR				
CONTROL	mean	76.88	232.95	417.63
(4)	S.D.	1.84	30.41	56.58
0.9J	mean	79.39*	296.20	380.39
(4)	S.D.	0.32	42.36	7.91
1.4J	mean	79.27	278.42	404.68
(4)	S.D.	1.08	41.71	27.46
ROD	mean	76.19	216.40	402.15
(4)	S.D.	2.37	12.56	39.05
72 HOUR				
CONTROL	mean	78.01	233.48	432.11
(4)	S.D.	0.92	8.73	26.12
0.9J	mean	80.57**	355.16 *	398.72
(3)	S.D.	0.63	51.29	31.81
1.4J	mean	79.79**	283.16*	411.75
(4)	S.D.	0.46	30.72	38.50
168 HOUR				
CONTROL	mean	78.03	229.82	458.52
(5)	S.D.	0.44	8.89	12.03
0.9J	mean	77.59	283.16**	384.45**
(5)	S.D.	1.64	28.61	32.62
1.4J	mean	78.42	293.68**	392.01*
(5)	S.D.	1.02	34.10	38.48
ROD	mean	77.72	238.43	445.84
(4)	S.D.	1.48	17.09	34.98

** $P<0.01$, * $P<0.05$ as compared to corresponding time control values.

Table 72

NON-LESIONED HEMISPHERE - OCCIPITAL CORTEX

		%WATER	Na^+ (mEq/Kg dry weight)	K^+ (mEq/Kg dry weight)
0 HOUR				
CONTROL	mean	77.72	226.07	439.63
(4)	S.D.	0.41	5.23	9.40
6 HOUR				
CONTROL	mean	77.88	235.77	437.39
(4)	S.D.	0.63	2.16	20.49
0.9J	mean	77.04	218.51	413.55
(4)	S.D.	0.59	13.00	21.94
1.4J	mean	77.53	220.98	412.08*
(4)	S.D.	1.12	27.19	7.15
24 HOUR				
CONTROL	mean	78.27	239.74	449.08
(4)	S.D.	0.43	9.77	11.09
0.9J	mean	77.16*	212.18*	425.52
(4)	S.D.	0.76	3.43	20.45
1.4J	mean	77.64	213.91	444.81
(4)	S.D.	0.88	24.07	43.99
48 HOUR				
CONTROL	mean	77.94	245.74	442.96
(4)	S.D.	0.68	19.98	12.96
0.9J	mean	76.75	226.95	405.45**
(4)	S.D.	0.89	22.18	13.79
1.4J	mean	77.85	218.42	418.82
(4)	S.D.	1.31	23.85	47.40
ROD	mean	76.09	208.17#	385.96#
(4)	S.D.	2.08	18.08	36.16
72 HOUR				
CONTROL	mean	77.40	230.82	416.92
(4)	S.D.	0.99	8.37	24.70
0.9J	mean	78.44	233.54	448.05
(3)	S.D.	0.81	14.71	48.98
1.4J	mean	78.50	230.74	437.88
(4)	S.D.	0.93	12.42	21.33
168 HOUR				
CONTROL	mean	78.35	237.72	467.83
(5)	S.D.	0.57	6.09	19.77
0.9J	mean	76.96	237.89	427.98
(5)	S.D.	1.34	12.72	30.57
1.4J	mean	77.99	238.88	443.01
(5)	S.D.	1.49	32.01	53.74
ROD	mean	77.15	227.49	432.62
(4)	S.D.	1.90	16.11	52.12

** $P<0.01$, * $P<0.05$ as compared to corresponding time control values.
# $P<0.05$ comparing rod value with corresponding time control value.

Table 73

MID-BRAIN

		%WATER	Na^+ (mEq/Kg dry weight)	K^+ (mEq/Kg dry weight)
0 HOUR				
CONTROL	mean	74.27	186.51	372.07
(4)	S.D.	0.38	1.86	7.59
6 HOUR				
CONTROL	mean	73.83	184.76	354.14
(4)	S.D.	0.57	6.42	6.98
0.9J	mean	75.16*	184.34	376.88*
(4)	S.D.	0.49	4.71	11.75
1.4J	mean	75.01	191.06	368.00
(4)	S.D.	0.96	11.51	13.44
24 HOUR				
CONTROL	mean	74.28	190.19	366.91
(4)	S.D.	0.81	7.00	14.76
0.9J	mean	74.35	186.72	363.66
(4)	S.D.	0.99	4.24	21.32
1.4J	mean	73.91	174.11	347.86
(4)	S.D.	1.71	6.51	31.78
48 HOUR				
CONTROL	mean	74.04	192.28	357.27
(4)	S.D.	0.57	16.38	22.45
0.9J	mean	74.52	193.20	354.81
(4)	S.D.	0.29	5.27	13.89
1.4J	mean	74.77	177.40	340.98
(4)	S.D.	0.44	16.92	44.70
ROD	mean	74.47	187.49	372.17
(4)	S.D.	0.29	5.35	11.16
72 HOUR				
CONTROL	mean	73.55	183.41	344.68
(4)	S.D.	0.54	12.14	8.69
0.9J	mean	74.33	190.62	358.40
(3)	S.D.	1.08	8.75	19.86
1.4J	mean	75.08	192.30	369.20
(4)	S.D.	1.02	7.69	22.60
168 HOUR				
CONTROL	mean	75.37	196.22	402.40
(5)	S.D.	0.48	7.23	14.13
0.9J	mean	74.83	207.88	384.92
(5)	S.D.	1.51	15.77	30.13
1.4J	mean	74.22*	204.75	362.34*
(5)	S.D.	0.98	17.31	24.80
ROD	mean	74.80	192.59	378.78
(4)	S.D.	0.82	6.35	19.57

* $P<0.05$ as compared to corresponding time control values.

Table 74

BRAIN STEM

		%WATER	Na^+ (mEq/Kg dry weight)	K^+ (mEq/Kg dry weight)
0 HOUR				
CONTROL	mean	71.78	169.69	317.76
(4)	S.D.	0.52	7.41	9.27
6 HOUR				
CONTROL	mean	71.71	174.10	319.81
(4)	S.D.	0.55	6.66	10.35
0.9J	mean	74.11	189.41	362.60
(4)	S.D.	2.68	26.29	51.13
1.4J	mean	72.83	176.66	324.66
(4)	S.D.	1.51	13.43	12.85
24 HOUR				
CONTROL	mean	71.72	170.82	321.86
(4)	S.D.	0.92	12.94	14.14
0.9J	mean	72.08	168.94	321.37
(4)	S.D.	1.29	7.64	27.05
1.4J	mean	71.62	169.13	310.26
(4)	S.D.	1.40	2.67	33.85
48 HOUR				
CONTROL	mean	71.32	172.85	306.39
(4)	S.D.	0.85	11.23	17.15
0.9J	mean	71.79	177.01	310.01
(4)	S.D.	0.75	3.61	7.26
1.4J	mean	72.51	169.10	304.24
(4)	S.D.	0.76	17.12	29.73
ROD	mean	72.39	170.91	327.84
(4)	S.D.	1.11	12.34	17.94
72 HOUR				
CONTROL	mean	70.65	166.33	305.38
(4)	S.D.	0.64	10.17	24.99
0.9J	mean	71.76	176.39	327.37
(3)	S.D.	1.31	1.36	0.07
1.4J	mean	73.24*	179.46	332.63
(4)	S.D.	1.28	9.82	23.13
168 HOUR				
CONTROL	mean	71.61	174.26	329.90
(5)	S.D.	1.57	7.21	19.46
0.9J	mean	71.26	174.27	332.92
(5)	S.D.	1.35	12.87	21.52
1.4J	mean	70.84	179.78	313.96
(5)	S.D.	1.42	11.91	24.01
ROD	mean	71.78	176.41	327.77
(4)	S.D.	1.40	8.47	24.59

* $P<0.05$ as compared with corresponding time control value

Table 75

CEREBELLUM

		%WATER	Na^+ (mEq/Kg dry weight)	K^+ (mEq/Kg dry weight)
0 HOUR				
CONTROL	mean	77.35	209.68	432.37
(4)	S.D.	0.57	4.93	11.80
6 HOUR				
CONTROL	mean	77.82	212.83	441.81
(4)	S.D.	0.51	10.08	7.97
0.9J	mean	76.95	198.49	416.26
(4)	S.D.	3.13	17.16	59.21
1.4J	mean	77.23	192.80**	411.67
(4)	S.D.	0.59	12.12	19.66
24 HOUR				
CONTROL	mean	77.28	207.16	429.81
(4)	S.D.	0.24	5.43	10.07
0.9J	mean	77.57	191.28	437.88
(4)	S.D.	0.28	4.96	11.55
1.4J	mean	76.91	192.39	425.09
(4)	S.D.	0.91	27.00	38.54
48 HOUR				
CONTROL	mean	77.83	223.16	438.98
(4)	S.D.	0.38	13.17	16.65
0.9J	mean	77.02*	208.49*	416.67*
(4)	S.D.	0.48	11.90	5.01
1.4J	mean	77.36	191.77*	411.39*
(4)	S.D.	0.31	18.55	12.34
ROD	mean	77.25	205.22	424.70
(4)	S.D.	0.48	4.60	16.24
72 HOUR				
CONTROL	mean	76.13	201.50	392.42
(4)	S.D.	0.58	3.24	9.35
0.9J	mean	77.09	215.16	415.94*
(3)	S.D.	0.78	11.75	11.11
1.4J	mean	77.55**	207.91	422.32*
(4)	S.D.	0.45	7.34	19.29
168 HOUR				
CONTROL	mean	77.33	211.46	439.85
(5)	S.D.	0.76	8.38	22.53
0.9J	mean	77.36	224.55	453.18
(5)	S.D.	0.79	10.27	12.26
1.4J	mean	77.34	217.90	433.93
(5)	S.D.	0.95	18.52	34.16
ROD	mean	77.61	220.27	452.72
(4)	S.D.	1.18	11.98	34.66

** $P<0.01$, * $P<0.05$ as compared to corresponding time control values.

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